MASTER'S THESIS

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Title: A multi-state model for the prognosis of non-mild acute pancreatitis

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A multi-state model for the prognosis of non-mild acute pancreatitis

Master thesis (TFM)

Master's degree in Statistics and Operations Research

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Esker txarreko izan nahi ez, eta esker oneko hitzak besterik ez ditudan honetan, lerrook eskerrik asko horiek guztiak adierazteko.

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Abstract

Acute pancreatitis (AP) is an inflammatory condition of the pancreas with low mortality in its mild forms. Nevertheless, the most severe forms, and consequently patients with AP admitted to Intensive Care Units (ICU), showed high mortality. In addition, prediction of AP mortality is not straightforward due to the low incidence of the most severe forms and because its fluctuating clinical course. Although several prediction score systems had been developed, all of them are complex and cumbersome to achieve and, moreover, present a high rate of false positive results. It is, consequently, of paramount importance to determine risk factors for AP so that an adequate prognosis of the disease can be established.

Motivated by data from an observational, prospective study of 286 patients with non-mild AP who entered the ICU of the Donostia University Hospital between 2001 and mid-2017, we propose a multi-state modeling approach to describe the evolution of patients with AP and at least one organ failure or local complications. An extension of the illness-death model is used allowing to take into account the disease-related events of interest, that is, entry to ICU, discharge from ICU and death due to AP.

The main goal of this joint project between the Donostia University Hospital and the Universitat Politècnica de Catalunya is the subject-specific management of the patients according to the observed progression of the disease. To this end the present study describes the course of AP patients and evaluates the effect of different prognostic factors on the multiple disease-related events, by means of non-parametric methods and Cox proportional hazards regression models with covariates that are fixed over time and with time-dependent covariates.

Keywords: multi-state model, prognosis, acute pancreatitis, survival analysis.

Introduction

Context of the study

This project is framed on survival analysis and event history analysis, subject areas that provide a set of statistical tools to study time-to-event data, either methods to analyze the time to a single event of interest, or time to several events.

The work is motivated by the "Epidemiología de la Pancreatitis Aguda en Medicina Intensiva del Hospital Universitario Donostia" (EPAMI-D) dataset. In this regard, we propose a multi-state modeling approach and our main contribution is hereby focused on modeling the course of the acute pancreatitis and on identifying prognostic factors of its evolution.

State of the art

Acute pancreatitis (AP)

Acute pancreatitis is a sudden inflammation and swelling of the pancreas, see Figure 1. It is a clinical entity with an increasing incidence [6] and is among the most common reasons for inpatient hospitalization for a gastrointestinal condition [7, 8]. This benign entity has a low overall mortality, but could be high in its more severe forms. Approximately 80% of patients have a short-lived, mild illness and recover promptly, whereas 20% have a more serious illness characterized by organ system failure, pancreatic necrosis, various infections, and death [9]. The mortality in patients with AP admitted in ICU ranges between 20-40% [9].

AP can be triggered by a variety of factors. The most common etiologies are gallstones and alcohol which comprises 60-85% of all incidents [11, 12]. Approximately 10-20% occur without a detectable cause and are considered "idiopathic". It is plausible that the characteristics and course of disease differ among etiologies.

According to the clinical course, the mortality of AP presents two peaks: early mortality, in the first 14 days, mainly due to Systemic Inflammatory Response Syndrome; and late mortality, after two weeks of evolution, mainly originated by infected necrosis [10, 13, 14]. Besides, regarding early mortality, there is a small subgroup of patients, whose clinical course is truly catastrophic [15]. These patients tend to die within the first few days (or even the first day) after presentation either because of respiratory failure or because of an overwhelming systemic inflammatory syndrome. These patients have recently been described as "fulminant

acute pancreatitis" patients.

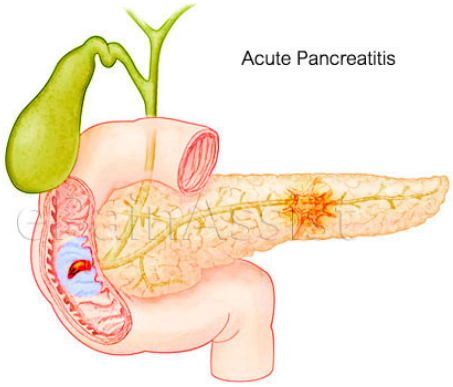


Figure 1: The pancreas and surrounding organs. The body of the pancreas appears sored and swollen

Since 2004, there was not a firm consensus in Spain on the way of facing this complex disease in ICU. The mortality of AP among different spanish ICUs was different. Besides, the difference in mortality with respect to the foreign units was striking. To a larger extent, the discrepancies between the hospitals and countries could be explained by: the wide variation in the characteristics of the patients, various ranges of disease severity, heterogeneity in patient populations, the clinical setting and influence of the administered treatment. However, there was not an agreement in Spain on the knowledge of AP and the inconsistency of spanish ICU outcomes was worrying.

In order to improve the situation, in 2004, all the Gastroenterology and Intensive Medicine societies in Spain reached a consensus on the diagnosis and treatment of AP in an ICU [17]. Then, subsequent guidelines have been published in Spain that offer some recommendations and make the management of AP in ICU more uniform.

Survival analysis (SA)

Survival analysis is a collection of statistical procedures intended to analyze time to event data. This type of data arises in a number of applied fields, such as medicine, biology, public health, epidemiology, engineering, economics, and demography.

Since the second half of the 20th century, survival analysis has mainly revolved around clinical applications and the scope of it has become wide. In fact, the benefits in the field of health have been innumerable.

This branch of statistics presents one peculiar feature, which it is known as censoring. For instance, in most medicine and public health studies there will inevitably be loss to follow-up and as a result, the available information of some individuals will be incomplete. This lack of information leads to considerable technical problems. A second feature which may be present is that of truncation. It occurs when we are only aware of individuals with event times in the observational window and no information is available about remainder subjects, in contrast to

censored subjects where there is at least partial information on it. In addition to censorship and truncation, the distribution of the outcome variable –time until an event occurs– is not symmetric. That being so, the normal law that is usually worked is not appropriate in the survival setting.

As stated, broad development has been made and there exists nowadays novel subdisciplines, e.g. multi-state models. Multi-state models may be considered as a generalization of the basic framework for dealing with survival data [4]. By means of these models another endpoints of interest, possibly competing, can be studied, besides overall survival. Competing risks models are as well, a special case of multi-state models.

There exists a vast literature on these subfields, research is still ongoing. Between 2000 and 2017, more than 200 and 900 methodological papers, regarding to multi-state and competing risks respectively, have been published in probability and statistical journals*. Figure 2 shows the increasing trend of published papers on this topic in the last 17 years.

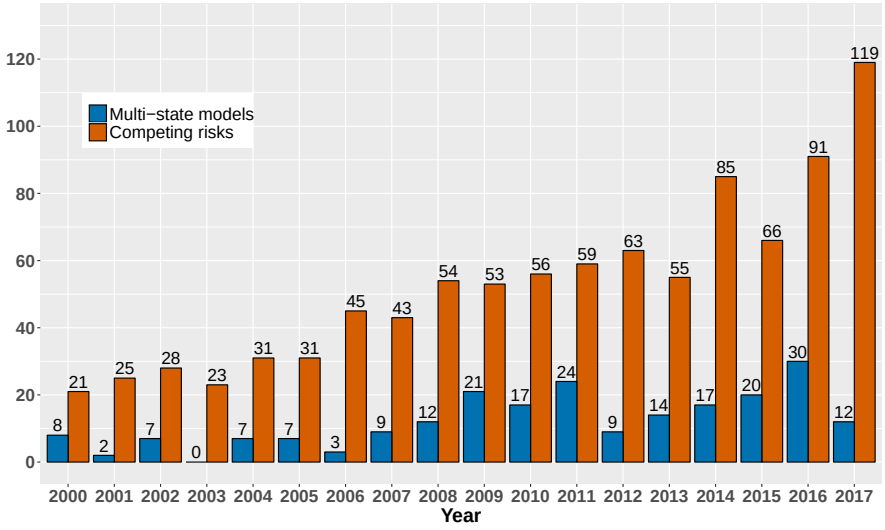


Figure 2: Evolution of published papers on multi-state models and competing risks in recent years

Goals

The goals of this joint project between the Donostia University Hospital and the Universitat Politècnica de Catalunya are of practical and theoretical nature.

The course of acute pancreatitis is characterized by the occurrence of several events on the same patient, such as ICU admission, recover from ICU, death, total recovery etc. These events determine several time-to-event endpoints and thus from the methodological point of

*A total of 220 and 948 papers identified by a search in Web of Science on February 23th, with the keyword *multi-state* models* and *competing risks* as a topic, from 2000 to 2017, restricted to subject area Statistics & Probability.

view, our aim is to apply a multi-state model describing the progression to each of the events. On the basis of this model, we intend to figure out some key points in the management of patients with AP in ICU:

- **Risk factors.** Which variables have higher influence in the course of a patient with AP?
- **Etiology.** Does the course of acute pancreatitis differ among different etiologies? So should biliary, alcoholic and idiopathic patients be treated as distinct entities?
- **Surgery.** What is the relationship between surgery and mortaliy? Is there any difference between early surgery and late surgery with respect to the mortality?
- **Length of stay.** Which is the influence of the time at which intermediate events occur? For instance, if a patient has been rapidly discharged from ICU, how fast will she/he be completely recovered?
- **Prognosis prediction.** Which is the clinical prognosis of a patient at a certain point of her/his course of illness? For example, which is the probability that a 60 years-old man who has been discharged from ICU after 2 weeks, get recovered?

Regarding clinical management, we believe that predicting which patients will have more severe disesase, as well as who might die, may be helpful in the triage of patients to high-intensity nursing units and in determining whether more aggressive therapy should be applied early in the clinical course. The approach might help in understanding the mechanisms of severe disease, identifying at-risk patients earlier, and developing therapies to mitigate disease severity. Secondly, the study of non-fatal events is important in what economy concerns; there may exist some factors that prolong hospitals stays and increases health care costs.

Furthermore, since this is a multidisciplinary work, it will be essential to be familiarized with the medical literature, and to share and communicate our results, on an ongoing basis, with other experts.

Outline

The project is divided into an introduction, five main chapters and the appendix. The current preface has introduced the reader to the problem and its main objectives. It has highlighted as well, the underlying motivation to carry out the work.

Chapter 1 provides the theoretical background that is used throught the analyses. It starts introducing the general features and notation for multi-state models and it follows reporting the analogy between the classical survival analysis and the more novel multi-state approach. It is shown that multi-state models are just an extension of the well-known time-to-event data models. Functions that totally characterize multi-state models are presented. Last, it is explained how each individual, under some assumptions, contributes to the likelihood function and how the Cox regression is modeled when one wishes to incorporate covariate information in the multi-state model.

Chapter 2 aims to describe the clinical problem. It gives the details of the dataset, called "Epidemiología de la Pancreatitis Aguda en Medicina Intensiva del Hospital Universitario Donostia" (EPAMI-D) and summarizes the general characteristics of the patients.

Chapter 3 illustrates the proposed multi-state model for the study at hand. For the case of this model, the explicit formulas of the transition probabilities —a measure of interest— are derived. In addition, it is explained how the data should be represented in `R` and a non-parametric analysis is carried out.

Chapter 4 devotes to the analyses and to the estimation of the prognostic factors for each of the events and it has two main parts. The first part involves a multi-state model analysis that takes into account baseline variables, and the second part involves analysis that considers one time-dependent variable, together with the baseline variables. Finally, the goodness of fit of the model is assessed.

Chapter 5 covers the final remarks and addresses those aspects which remain to be completed.

Finally, an appendix is displayed as a complementary of the report. It consists of some calculations, further outputs of the analyses, the clinical overview and the `R` code. We think that this add-on will be helpful for the ones that might want to deepen more.

Chapter 1

Theoretical background

In this chapter we describe methods of survival analysis from the multi-state models point of view. Much of the theory is taken from Aalen et al. (2008) [19] and Beyersmann et al. (2012) [20].

First, we will think of the standard survival analysis, that studies a time T until one single event of interest, as a basic two-state multi-state model. Then we will consider competing risks models which extend the study of a unique endpoint to multiple ones. Finally, we will turn to more general multi-state models. A key issue is that multi-state models* can be seen as being realized as a "nested series of competing risks experiments". We therefore build on competing risks methodology.

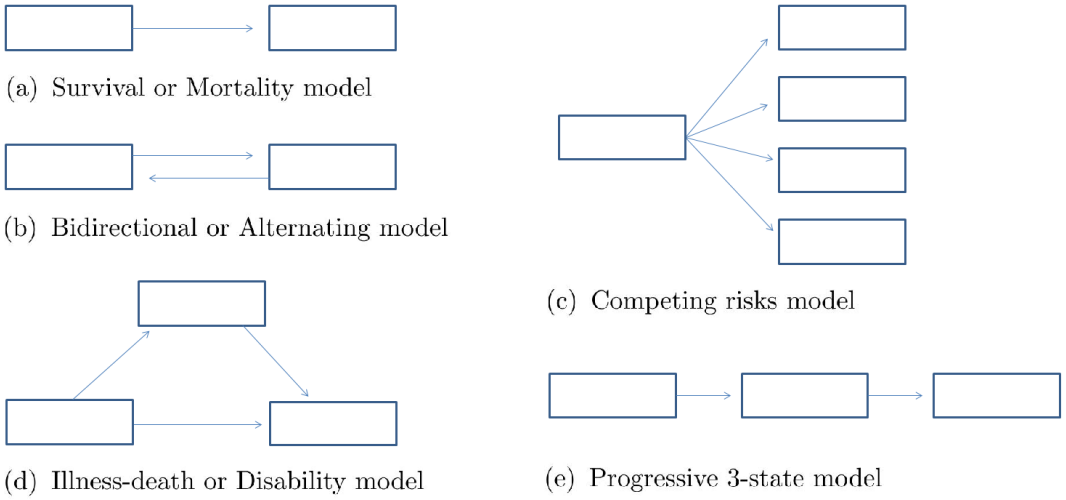
1.1 General features of multi-state models

Multi-state models are models for stochastic processes, which represent the evolution of an item (e.g. a patient, a device) along time. The item may visit a number of states along its progress and, so, the multi-state model indicates the existing states as long as the allowed transitions among them. We denote:

- **Transition:** a change of state, the occurrence of an event.
- **States structure:** specifies the states and which transitions from state to state are possible. It is practical to make a graphical representation of the different possible events (states) linked with arrows representing the difference paths (transitions) between events. Some examples are shown in Figure 1.1.
- **Statistical model:** specifies the states structure and the form of the hazard function for each possible transition.

The states can be of two types. If there are no transitions going out from the state is called absorbing. After entry into the state the process stays in it forever. Otherwise, the state is

*Markovian



(a) Survival or Mortality model

(b) Bidirectional or Alternating model

(c) Competing risks model

(d) Illness-death or Disability model

(e) Progressive 3-state model

Figure 1.1: Standard multi-state models

named transient.

We also note that the process is said to be time-inhomogeneous if transitions depend on the time interval $[s, t]$. In contrast, a time-homogeneous process makes the more restrictive assumption that the transitions only depend on the length of the time interval $d = t - s$.

It is usually assumed in practice that the model under study satisfies the Markov condition. Later we will go through Markovian multi-state models a bit more in depth. If the Markov assumption is violated, Semi-Markov or Non-Markovian models are fitted to the data. The analysis of Non-Markov models is a quite active research field.

1.2 Survival model

It is the simplest multi-state model with two states, see Figure 1.1 (a). An item is in the initial state 0 (e.g. "Alive") at time origin. At some later random time T, the item moves to the absorbing state 1 (e.g. "Death").

To find out about the event time T, we define a stochastic process X. We write $X(t)$ for the state occupied by the item at time $t \geq 0$, $X(t) \in \{0, 1\}$. T is the smallest time at which the process is not in the initial state 0 anymore,

$$T := \inf\{t : X(t) \neq 0\}.$$

This relationship between the stochastic process $(X(t))_{t\geq 0}$ and the event time T is shown in Figure 1.2. For illustration, consider an item with event time $T = 52$. This item will be in state 0 for all times $t \in [0, 52)$ and in state 1 for all times $t \geq 52$. Note that the state occupied at the event time T is the absorbing state 1, i.e., $X(T) = X(52) = 1$. This definition implies that the sample paths of the stochastic process, i.e. $[0, \infty) \ni t \mapsto X(t)$, are piecewise constant right-continuous.

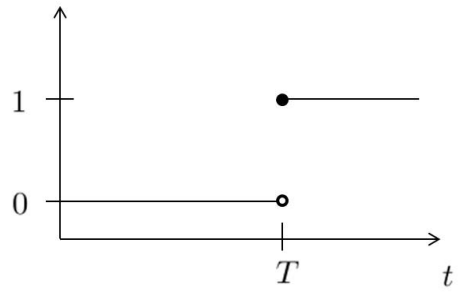


Figure 1.2: Stochastic process $(X(t))_{t\geq 0}$ and the event time T

The statistical analysis of T, absolutely continuous, is based on the hazard $\alpha(t)$ attached to the distribution of T,

$$\alpha(t) := \lim_{\Delta t \to 0^+} \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t}.$$

We can think of $\alpha(t)\mathrm{d}t$ as the instantaneous risk of occurring the event in the interval $[t, t+\mathrm{d}t)$, knowing that it was not yet occurred for that time.

Due to the dynamic nature of survival data, a characterization of the distribution by the hazard function is generally very convenient. In fact, the hazard function does not change when conditioning, it is already conditioned on survival time.

Furthermore, knowing the cumulative hazard $A(t)$,

$$A(t) := \int_0^t \alpha(u)\mathrm{d}u,$$

it suffices to recover the distribution function of T,

$$F(t) := 1 - S(t) := P(T \leq t) = 1 - \exp(-A(t)), \tag{1.1}$$

where $S(t) = P(T > t)$ is the survival function of T.

A useful notion is product integration. Since $\mathrm{d}A(u) = \alpha(u)\mathrm{d}u = P\left(T \in [u, u + \mathrm{d}u) \mid T \geq u\right)$, we may write,

$$1 - \mathrm{d}A(u) = P\left(T \geq u + \mathrm{d}u \mid T \geq u\right). \tag{1.2}$$

The survival function should then be an infinite product over conditional probabilities of (1.2). We call such an infinite product, a product integral and write $\prod$. So,

$$S(t) = \prod_0^t (1 - \mathrm{d}A(u)))^* \tag{1.3}$$

$$\approx \prod_{k=1}^{K} (1 - \Delta A(t_k)) \approx \prod_{k=1}^{K} P(T > t_k \mid T > t_{k-1}), \tag{1.4}$$

where $0 = t_0 < t_1 < t_2 < \ldots < t_{K-1} < t_K = t$ partitions the time interval $[0, t]$ and $\Delta A(t_k) = A(t_k) - A(t_{k-1})$. Now, the right hand side of (1.1) can simply be seen as a solution of the product integral in (1.3). The product integral itself shows up with the Kaplan-Meier estimator of the survival function. And, when we move from survival analysis to competing risks and multi-state models the product integral is in a matrix-valued form.

1.2.1 Observable data

Survival and event history data occur over the course of time, and a data analysis is regularly performed before or without knowing all failure times, e.g. a clinical study might be closed with patients not experiencing the event, or individuals may drop out of a study. This leads to incomplete observations and is known as right-censoring. We only know the actual failure time to be greater than a certain value.

In the presence of right-censoring, let $T_1,\ T_2,\ \ldots,\ T_n$ be a sample of (partially observed) times and $C_1,\ C_2,\ \ldots,\ C_n$ random censoring. We assume that C_i is independent of T_i for all $i = 1, 2, \ldots, n$, or at least that the distribution of survival times T provides no information about the distribution of censorship times C and vice versa, i.e. non-informative censoring. Then the observable data is $(U_1, \delta_1),\ (U_2, \delta_2),\ \ldots,\ (U_n, \delta_n)$ where

$$U_i = \min\{T_i, C_i\}, \qquad \delta_i = \mathbb{1}_{\{T_i \leq C_i\}} = \begin{cases} 1, & T_i \leq C_i, \\ 0, & T_i > C_i. \end{cases}$$

The random variable δ_i is the no-censorship indicator, although it is usually known as the censorship indicator.

Observation In the presence of censoring the hazard remains "undisturbed". For this reason, it is said that survival analysis is hazard-based. What is the probability of observing the actual event time in the small time interval $[t, t+\mathrm{d}t)$, conditional on the fact that neither event nor censoring have happened before t, $P(t \leq T < t + \mathrm{d}t, T \leq C | \min\{T, C\} \geq t) = P(t \leq U < t + \mathrm{d}t, \delta = 1 | U \geq t)$?

The interval $[t, t + \mathrm{d}t)$ is so short that, assuming T and C to be different, at most one is in $[t, t+\mathrm{d}t)$: if the event occurs in $[t, t+\mathrm{d}t)$, it will be observed (still supposing $U = \min\{T, C\} \geq$

*When $A(t)$ is absolutely continuous, using that for small $\mathrm{d}u$, $\exp(-\alpha(u)\mathrm{d}u) \approx 1 - \alpha(u)\mathrm{d}u$, we have that: $S(t) = \prod_0^t (1 - \mathrm{d}A(u)) = \prod_0^t (1 - \alpha(u)\mathrm{d}u) = \exp\left(-\int_0^t \alpha(u)\mathrm{d}u\right) = \exp(-A(t))$

t). Because C and T are independent, the probability that the event occurs in $[t, t + \mathrm{d}t)$, conditional on $U \geq t$, is the same as in the absence of censoring,

$$\alpha(t) \cdot \mathrm{d}t = P(T \in [t, t + \mathrm{d}t) \mid T \geq t) = P(T \in [t, t + \mathrm{d}t), T \leq C | \min\{T, C\} \geq t),$$

as a consequence, we may estimate the instantaneous hazard function from censored data. Following we will see that using product integration, this results in an estimation of the survival function.

1.2.2 Estimation

A common approach to survival estimation is to consider counting processes. A counting process counts the number of observed events during a time period. Thus, since in survival analysis we are looking at the occurences of events, it is natural to count them as they occur, and use this information for estimation purposes.

In this manner, we define the following stochastic processes,

- $N^i(t)$ and $N(t)$, $t > 0$ by:

$$N(t) := \sum_{i=1}^{n} \mathbb{1}_{\{U_i \leq t,\ \delta_i = 1\}} = \sum_{i=1}^{n} N^i(t)$$

  which is counting the number of events observed on or before t. This is a counting process.

- $Y^i(t)$ and $Y(t)$, $t > 0$ by:

$$Y(t) := \sum_{i=1}^{n} \mathbb{1}_{\{U_i \geq t\}} = \sum_{i=1}^{n} Y^i(t)$$

  where $Y(t)$ is the number of items at risk just before t.

Figure 1.3 illustrates the stochastic processes $N^i(t)$ and $Y^i(t)$.

Now, let $\Delta A(t)$ and $\Delta N(t)$ be, $A(t) - A(t^-)$ and $N(t) - N(t^-)$ respectively*. Then, a natural estimator of $\Delta A(t)$ is given by

$$\Delta \widehat{A}(t) = \frac{\Delta N(t)}{Y(t)},$$

that is number of individuals observed to "fail" at t, over number of individuals at risk just prior to t. Hence, the estimator of the cumulative hazard is given by

$$\widehat{A}(t) = \sum_{k=1}^{K} \frac{\Delta N(t_k)}{Y(t_k)},$$

*The notation t^- stands for: "just prior to time t".

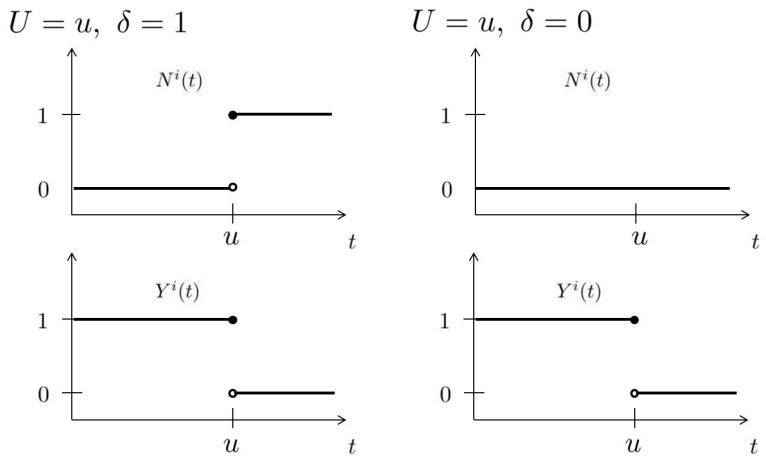


Figure 1.3: $N^i(t)$ and $Y^i(t)$ stochastic processes for an individual i. Left plots, the event is observed at time u. Right plots, the event is censored at time u. $N^i(t)$ is non-decreasing, right-continuous stepwise function and $Y^i(t)$ non-increasing stepwise function

if $0 < t_1 < t_2 < \ldots < t_{K-1} < t_K \leq t$ is the ordered sequence of the observed event times. $\widehat{A}(t)$ is the Nelson-Aalen estimator and if we plug this into the product integral we obtain the Kaplan-Meier estimator of $S(t)$.

$$\widehat{S}(t) = \prod_0^t \left(1 - \mathrm{d}\widehat{A}(u)\right) = \prod_{k=1}^K \left(1 - \Delta\widehat{A}(t_k)\right)$$

1.3 Competing risks model

Within the framework of multi-state models, the two-state survival model may now be generalized by introducing several competing absorbing states which represent the possible event types. Occurrence of a competing event is modelled by a transition into the corresponding competing event state, see Figure 1.1 (c).

Supposing that there are J competing events, we denote again $X = \{X(t) : t \geq 0\}$, being $X(t)$ the state occupied by the item at time t and we define as well, $\mathcal{S} = \{0, 1, \ldots, J\}$ the state space. $X(t) = 0$ if the item is still event-free at time t and $X(t) = h$, $h = 1, \ldots, J$, if the event type h has occurred in $[0, t]$. As before, the event time T is the smallest time at which the process is not in the initial state anymore, $T := \inf\{t : X(t) \neq 0\}$.

For each competing event h, the cause-specific hazard is defined as

$$\begin{aligned}\alpha_{0h}(t) &:= \lim_{\Delta t \to 0^+} \frac{P(t \leq T < t + \Delta t, X(T) = h \mid T \geq t)}{\Delta t} = \\ &= \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} P(X(t + \Delta t) = h \mid X(t) = 0), \quad h = 1, \ldots, J.\end{aligned}$$

It describes the instantaneous risk of experiencing the transition $0 \to h$. Thus $\alpha_{0h}(t) \cdot \mathrm{d}t$ indicates the probability that a type h event happens in the small interval $[t, t+\mathrm{d}t)$, conditional on the fact that no event (of any type) has happened before t.

1.3.1 Observable data

Competing risks data consist of a tuple of three components. In addition to the $(U_i,\ \delta_i)$ pair for each $i = 1, \ldots, n$ observation, the event type has to be considered. In this way, the observed data are given by,

$$\{(U_i,\ \delta_i,\ \delta_i X(U_i)),\, i = 1, 2, \ldots, n\}.$$

Observation Competing risks are the rule rather than the exception in epidemiological studies. Studies ought to check whether censoring is informative or not. When the censored individuals are not representative for the individuals still at risk, for instance, when censored individuals are those with low risk of dying, competing events should be acknowledged.

Since competing risks are a particular case of multi-state models, estimation and inference will be introduced in the next section.

1.4 Multi-state models

Multi-state models, in general, allow for modelling both the occurrence of different event types and the occurrence of subsequent events. To characterize, we require $X = \{X(t) : t \geq 0\}$ stochastic process, $\mathcal{S}$ discrete state space where $X(t)$ has values, $X(t) \in \mathcal{S}$, and a filtration, $\mathcal{F}_t = \sigma\{X(s) : s \leq t\}$, i.e. $\sigma-$algebra consisting of the observation of the process over the interval $[0, t]$, that is, it contains the history (the information of the course) of the process up to time t.

The law of a multi-state process is defined by its finite dimensional distribution and is fully characterized through either one of the following three functions:

- Transition probability between state l and state j for $s \leq t$:

  $$P_{lj}(s, t; \mathcal{F}_{s^-}) := P(X(t) = j \mid X(s) = l; \mathcal{F}_{s^-}),$$

  probability of being in state j at time t, conditioned on the history up to time s and that the item was in state l at time s, i.e. probability of experiencing $l \to j$ transition.

- Transition intensities:

  $$\alpha_{lj}(t; \mathcal{F}_{t^-}) := \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} P_{lj}(t, t + \Delta t; \mathcal{F}_{t^-}),$$

  the tantamount of cause-specific hazard function.

- Cumulative (integrated) transition intensities,

$$A_{lj}(t; \mathcal{F}_{t^-}) := \int_0^t \alpha_{lj}(u; \mathcal{F}_{u^-}) \mathrm{d}u.$$

Each one of the above transitions involves many time and state-parameters which might make the estimation hard, or even unfeasible. For this reason some assumptions are usually considered, such as the Markov assumption.

1.4.1 Markov models

The Markov property is a key assumption for the estimation techniques that we discuss. In essence, the Markov property means that the future course of an item depends on the past only via the current time and the state currently occupied by the item. It implies that the past and the future are conditionally independent given the present.

$$P(X(t) = j \mid X(s) = l; \mathcal{F}_{s^-}) = P(X(t) = j \mid X(s) = l),\ s \leq t.$$

Transition functions depend on $\mathcal{F}_{s^-}$ only via $X(t^-)$. Loosely speaking, we can think of it as that the present state contains all the memory.

Hence, the instantaneous risk of making a transition from l to j in a small time interval at t is given by $\alpha_{lj}(t) = \lim_{\Delta t \to 0^+} \frac{P_{lj}(t, t+\Delta t)}{\Delta t}$, for $l \neq j$. What's more, fixed l, $\sum_{j \in \mathcal{S}} \alpha_{lj}(t) = 0$, and then we define $\alpha_{ll}(t)$ as

$$\alpha_{ll}(t) := -\sum_{j \neq l} \alpha_{lj}(t). \tag{1.5}$$

1.4.2 Estimation

The setting is similar to the survival model situation. We analogously introduce notation connected to occupation of states in the model and possible transitions between them:

- The counting process $N_{lj}(t)$, $t > 0$ and $l, j \in \mathcal{S}$, defined by:

$$N_{lj}(t) := \sum_{i=1}^{n} \mathbb{1}_{\{U_i \leq t,\ \delta_i = 1,\ X^{(i)}(0) = l,\ X^{(i)}(t) = j\}} = \sum_{i=1}^{n} N_{lj}^i(t) \tag{1.6}$$

  counts the number of direct $l \to j$ transitions observed in $[0, t]$.

- The risk process $Y_l(t)$, $t > 0$ and $l \in \mathcal{S}$, defined by:

$$Y_l(t) := \sum_{i=1}^{n} \mathbb{1}_{\{U_i \geq t,\ X^{(i)}(t^-) = l\}} = \sum_{i=1}^{n} Y_l^i(t) \tag{1.7}$$

  provides the number of items in state l under observation just before time t.

We also write $\Delta N_{lj}(t) := N_{lj}(t) - N_{lj}(t^-)$ for the increments of $N_{lj}(t)$, i.e., the number of $l \to j$ transitions observed "exactly" at time t.

We now derive the Nelson-Aalen estimator of $A_{lj}(t) = \int_0^t \alpha_{lj}(u)\mathrm{d}u$: if we do not observe the $l \to j$ transition at t ($\Delta N_{lj}(t) = 0$), then the increment $\alpha_{lj}(t)\mathrm{d}t$ is 0. On the contrary, if we do observe the $l \to j$ transition at t ($\Delta N_{lj}(t) > 0$), we estimate the conditional transition probability as the ratio of the number of $l \to j$ transitions, $\Delta N_{lj}(t)$, divided by the number of items at risk just prior to the transition time t, $Y_l(t)$. Summing up over these increments yields the Nelson-Aalen estimator,

$$\widehat{A}_{lj}(t) := \int_0^t \frac{\mathrm{d}N_{lj}(u)}{Y_l(u)} = \sum_{s \le t} \frac{\Delta N_{lj}(s)}{Y_l(s)}, \quad l, j \in \mathcal{S},\ l \neq j, \tag{1.8}$$

where the summation is over all observed event times in $[0, t]$ and $\widehat{A}_{ll}(t) = -\sum_{j:j\neq l} \widehat{A}_{lj}(t)$.

Finally, we wish to estimate the transition probabilities matrix $\mathbf{P}(s,t) := (P_{lj}(s,t))_{l,j}$, $l, j \in \mathcal{S}$. We shall write as well, $\mathbf{A}(t) := (A_{lj}(t))_{l,j}$, $l, j \in \mathcal{S}$. The aim is to show that $\mathbf{P}(s,t)$ can be computed as a continuous matrix-valued product over terms

$$\mathbf{I} + \mathrm{d}\mathbf{A}(u),$$

where u ranges from s to t, where we have written $\mathbf{I}$ for the $(J+1) \times (J+1)$ identity matrix, J total number of states, and where $\mathrm{d}\mathbf{A}(u)$ is defined element wise as $\mathrm{d}(A_{lj}(u))_{l,j} = (\alpha_{lj}(u))_{l,j}\mathrm{d}u$.

Subsequent expression explains why we have defined $\alpha_{ll}(t)$ as in equation (1.5) and why we have to consider a product over terms $\mathbf{I} + \mathrm{d}\mathbf{A}(u)$ too:

$$1 + \mathrm{d}A_{ll}(u) = 1 - \sum_{j:j\neq l} P\left(X((u+\mathrm{d}u)^-) = j \mid X(u^-) = l\right) = P\left(X((u+\mathrm{d}u)^-) = l \mid X(u^-) = l\right).$$

For Markov processes, we have the following identities, known as the Chapman-Kolmogorov equations

$$\mathbf{P}(s,t) = \mathbf{P}(s,v)\mathbf{P}(v,t), \quad v \in (s,t).$$

Using these equations we get that,

$$\begin{aligned}
\mathbf{P}(s, t+\Delta t) - \mathbf{P}(s,t) &= \mathbf{P}(s,t)\mathbf{P}(t,t+\Delta t) - \mathbf{P}(s,t) \\
&= \mathbf{P}(s,t)\left(\mathbf{P}(t,t+\Delta t) - \mathbf{I}\right) \\
&\approx \mathbf{P}(s,t)\boldsymbol{\alpha}(t)\Delta t,
\end{aligned}$$

where

$$\boldsymbol{\alpha}(t) = \lim_{\Delta t \to 0^+} \frac{1}{\Delta t}\left(\mathbf{P}(t, t+\Delta t) - \mathbf{I}\right).$$

Thus the Kolmogorov forward equation holds,

$$\frac{\partial}{\partial t}\mathbf{P}(s,t) = \mathbf{P}(s,t)\boldsymbol{\alpha}(t), \tag{1.9}$$

which can be expressed as

$$\mathbf{P}(s,t) = \mathbf{I} + \int_s^t \mathbf{P}(s,u^-)\mathrm{d}\mathbf{A}(u). \tag{1.10}$$

We make a partition of the time interval $[s,t]$, $s = t_0 < t_1 < t_2 < \ldots < t_{K-1} < t_K = t$, and using the Chapman-Kolmogorov equation recursively, we obtain

$$\mathbf{P}(s,t) = \mathbf{P}(t_0,t_1)\mathbf{P}(t_1,t_2)\ldots\mathbf{P}(t_{K-1},t_K),$$

and by using equation (1.10), we get the approximation

$$\mathbf{P}(s,t) \approx \prod_{k=1}^{K}\{\mathbf{I} + (A(t_k) - A(t_{k-1}))\} = \prod_{k=1}^{K}\left(\mathbf{I} + \Delta A(t_k)\right). \tag{1.11}$$

Computing the approximation on the right hand side of (1.11) for ever finer partitions of $[s,t]$, $\mathbf{P}(s,t)$ approaches a limit, which results in the matrix-valued product integral $\prod_{u\in(s,t]}(\mathbf{I} + \mathrm{d}\mathbf{A}(u))$.

As a result, we get the Aalen-Johansen estimator of the transition probabilities matrix, by replacing $\mathbf{A}(u)$ with the matrix $\widehat{\mathbf{A}}(u)$ of Nelson-Aalen estimator,

$$\widehat{\mathbf{P}}(s,t) = \prod_{s<t_k\leq t}\left(\mathbf{I} + \Delta\widehat{\mathbf{A}}(t_k)\right),$$

where t_k are observed transition times in $(s,t]$. The Aalen-Johansen estimator is often also called the empirical transition matrix. In chapter 3 we will derive explicit expressions for the elements of $\mathbf{P}(s,t)$ and $\widehat{\mathbf{P}}(s,t)$ matrices corresponding to our multi-state model.

1.5 Likelihood function

The likelihood function can be written in terms of the $\alpha_{lj}(\cdot)$ and the $P_{lj}(\cdot,\cdot)$ under the assumptions of: ignorability, conditional on the state at the first observation time T_0, independent X^i processes and Markov assumption. The ignorability condition says that the mechanism leading to incomplete data is ignorable, meaning that the likelihood treating the observation process as non-random leads to the same inference as the full likelihood. The condition works, for instance, in the cases where the observation process (also random) is completely independent of the processes of interest X. Besides, we consider:

- n individuals under study with individual multi-state data subject to independent right-censoring.
- Each individual i followed up to a τ_i time.

- The multi-state processes $X^i(t)$ observed over intervals $[0, \tau_i]$, for $i = 1, \ldots, n$.
- Exactly observed transition times, $T_1^i,\ T_2^i,\ \ldots,\ T_K^i \leq \tau_i$.

The contribution to the likelihood function of the i^{th} individual conditional on $X^i(0)$ is:

$$\mathcal{L}\left(\alpha(\cdot),\ X\right) = \left[\prod_{k=0}^{K-1} P_{X(T_k),X(T_k)}\left(T_k, T_{k+1^-}\right) \alpha_{X(T_k),X(T_{k+1})}\left(T_{k+1}\right)\right] P_{X(T_K),X(T_K)}\left(T_K, \tau\right).^* \quad (1.12)$$

1.6 Statistical model specification

Statistical models are usually obtained by specifying the class of transition intensities $\alpha_{lj}^i(t)$ for each individual i. There are several approaches such as parametric methods, smooth non-parametric approaches or Bayesian approaches which lead to a wide range of statistical models. In this work we will restrict our attention on the semi-parametric approach in order to quantify transition intensities and assess their dependence on covariates.

Then, we have modelled the effect of covariates using the Cox proportional hazards model [22]. In consequence, the transition intensity $\alpha_{lj}^i(t)$ for transition $l \to j$, for an individual i with covariate values $\mathbf{Z}^i(t) = (Z_1^i(t), \ldots, Z_p^i(t))$ is modelled as

$$\alpha_{lj}^i(t \mid \mathbf{Z}) = \alpha_{lj,0}(t) \exp(\boldsymbol{\beta}_{lj}^T \mathbf{Z^i(t)}),$$

where $\boldsymbol{\beta}_{lj}$ is a vector of regression coefficients and $\alpha_{lj,0}(t)$ is the baseline $l \to j$ transition intensity, a transition intensity of an individual with profile $\mathbf{Z} = \mathbf{0}$, assumed common for all individuals.

This regression model has a multiplicative structure. In fact, the effect of a covariate Z_m^i $m = 1, \ldots, p$ in $l \to j$ transition, is described by factors of proportionality $\exp(\beta_{lj,m})$ which is a commonly used effect measure known as the hazard ratio (HR).

$$\text{HR} = \frac{\alpha_{lj}(t \mid \mathbf{Z} = (0, \ldots, 0, Z_m, 0, \ldots, 0))}{\alpha_{lj}(t \mid Z = (0, \ldots, 0))} = \exp(\beta_{lj,m}),$$

it relates $\alpha_{lj}(t \mid \mathbf{Z})$ at moment t of an individual with profile Z_m with $\alpha_{lj,0}(t)$ at the same time of an individual with profile $\mathbf{Z} = \mathbf{0}$.

Moreover, the Cox's model is said to be semi-parametric due to the baseline hazard is completely unspecified.

1.6.1 Inference for Cox multi-state model

The inference is based on the likelihood (1.12) and it leads to the so-called Cox's partial likelihood function:

*For the ease of notation, we have suppressed the index i.

$$\mathcal{L}(\boldsymbol{\beta}) = \prod_{\substack{\text{transition} \\ l \to j}} \prod_{\substack{i=1 \\ \delta_{lj,i}=1}}^{n} \frac{\exp(\boldsymbol{\beta}_{lj}^T \mathbf{Z}^i(t_{lj,i}))}{\sum_{h \in R_l(t_{lj,i})} \exp(\boldsymbol{\beta}_{lj}^T \mathbf{Z}^h(t_{lj,h}))}, \tag{1.13}$$

where $t_{lj,i}$ is the failure or censoring time of individual i for transition $l \to j$, $\delta_{lj,i} = 1$ if individual has an event for transition $l \to j$, 0 otherwise, and where $R_l(t)$ is the risk set of state l at time t, i.e. the set of individuals who are in state l at time t.

Equation (1.13) is a product over the transitions and over the event times, of a quotient that compares the $l \to j$ transition intensity of an individual with the event at t_{lj} to the transition intensity of all the individuals at risk at t_{lj}. Note that the baseline hazard cancels out.

Once the coefficients of the explanatory variables, $\boldsymbol{\beta}$, are estimated by maximizing the partial likelihood (1.13), the estimates $\hat{\boldsymbol{\beta}}$ are used in Breslow's estimate of the baseline cumulative $l \to j$ transition intensity,

$$\widehat{A}_{lj,0}(t) = \sum_{\substack{i=1 \\ t_{lj,i} \leq t}}^{n} \frac{d_{lj,i}}{\sum_{l \in R_l(t_{lj,i})} \exp(\boldsymbol{\beta}_{lj}^T \mathbf{Z}^h(t_{lj,h}))}. \tag{1.14}$$

The key feature for obtaining a likelihood allowing for simple estimation is the extent to which different transitions share parameters. If the transitions do not share parameters, each possible transition can be studied separately. Also, transition hazards might be assumed to be proportional, considering simultaneously by means of proportional hazards models.

Example

As an illustration let consider a competing risk model with two causes, see Figure 1.4 and Table 1.1.

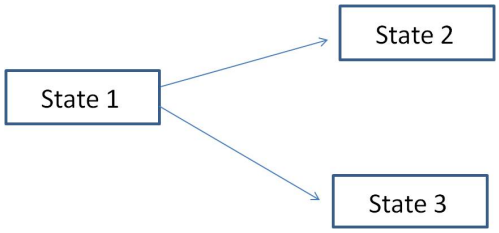


Figure 1.4: Two-cause competing risk (multi-state) model

In this instance some plausible questions could arise: is the risk of occurring the "Cause 1" greater for the women than men? In the case of "Cause 2", does the women have less chance than men of experiencing this "Cause 2"?

So to handle these questions and specially to measure how great are the risks, we could use Cox's proportional hazards model for one of the each two mutually exclusive events, "Cause 1" and "Cause 2".

id i	From	to	Tstart	Tstop	time $t_{lj,i}$	status $\delta_{lj,i}$	Gender.1 Z^i_{12}	Gender.2 Z^i_{13}
1	1	2	0	8	8	0	1	0
1	1	3	0	8	8	0	0	1
2	1	2	0	4	4	1	1	0
2	1	3	0	4	4	0	0	1
3	1	2	0	5	5	0	0	0
3	1	3	0	5	5	1	0	0

Table 1.1: Fictitious data in long format. $Z^i_{lj} = 1$ stands for female

The Cox's model describing the transition intensities to "Cause 1" (State 2) and "Cause 2" (State 3), and subject to covariate Z = Gender are formulated as:

$$\begin{aligned} &\textbf{Model for "Cause 1":} && \alpha_{12}(t) = \alpha_{12,0}(t)\exp(\beta_{12}Z), \\ &\textbf{Model for "Cause 2":} && \alpha_{13}(t) = \alpha_{13,0}(t)\exp(\beta_{13}Z), \end{aligned}$$

where $\alpha_{12,0}(t)$ and $\alpha_{13,0}(t)$ are baseline cumulative transition intensities and, β_{12} and β_{13} regression coefficients for the gender covariate effect Z.

There is another way of writing these models that is appropriate looked at from a practical standpoint. In **R**, as in Table 1.1, each individual will have a row for each transition that the individual is at risk. Then in order to model the effect of a covariate, which can be different for each transition, one creates transition specific dummy covariates. For this reason an alternative way of expressing these models is using covariates specific to each transition 1→2 and 1→ 3, Z_{12} and Z_{13}.

$$\begin{aligned} &\textbf{Model for "Cause 1":} && \alpha_{12}(t) = \alpha_{12,0}(t)\exp(\theta Z_{12}), \\ &\textbf{Model for "Cause 2":} && \alpha_{13}(t) = \alpha_{13,0}(t)\exp(\gamma Z_{13}), \end{aligned}$$

where $\alpha_{12,0}(t)$ and $\alpha_{13,0}(t)$ are baseline cumulative transition intensities, $\mathbb{Z}_{12}$ and $\mathbb{Z}_{13}$ are the transition-specific covariates for the gender covariate Z and, θ and γ are coefficients to estimate for the gender covariate in each transition.

Let us estimate the previous coefficients by means of the partial likelihood. First unless not indispensable but helpful we sum up the data in Table 1.4.

- Three individuals, $i = 1, 2, 3$ and, two transitions $1 \to 2$ and $1 \to 3$.
- Exactly observed transition times: $t_{12,(1)} = t_{12,2} = 4$ and $t_{13,(2)} = t_{13,3} = 5$. Putting into words, the first individual does not experience any event and is censored at time 8, the second individual experiences the "Cause 1" at time 4 and the third individual experiences the "Cause 2" at time 5.
- Risk sets: $R_1 = \{1, 2, 3\}$ and $R_2 = \{1, 3\}$.

We now derive the partial likelihood,

$$\begin{aligned}\mathcal{L}(\beta_{12},\beta_{13}) &= \prod_{\substack{\text{transition}\\ l\to j}} \prod_{\substack{i=1\\ \delta_{lj,i}=1}}^{3} \frac{\exp(\beta_{lj}Z^i(t_{lj,i}))}{\sum_{h\in R_l(t_{lj,i})}\exp(\beta_{lj}Z^h(t_{lj,h}))}\\ &= \underbrace{\frac{\exp(\beta_{12}\cdot 1)}{\exp(\beta_{12}\cdot 1)+\exp(\beta_{12}\cdot 1)+\exp(\beta_{12}\cdot 0)}}_{t_{12,2}=4}\cdot\underbrace{\frac{\exp(\beta_{13}\cdot 0)}{\exp(\beta_{13}\cdot 1)+\exp(\beta_{13}\cdot 0)}}_{t_{13,3}=5}\\ &= \frac{e^{\beta_{12}}}{2e^{\beta_{12}}+1}\frac{1}{e^{\beta_{13}}+1}\end{aligned}$$

Maximizing $\mathcal{L}(\beta_{12},\beta_{13})$ we obtain the estimates for β_{12} and β_{13}, for which numerical methods are needed in this example. Then, the measure that is named hazard ratio,

$$\begin{aligned}\text{HR}_1 &= \frac{\alpha_{12}(t\mid Z=1)}{\alpha_{12,0}(t)} = \exp(\beta_{12}) \qquad \text{for "Cause 1"},\\ \text{HR}_2 &= \frac{\alpha_{13}(t\mid Z=1)}{\alpha_{13,0}(t)} = \exp(\beta_{13}) \qquad \text{for "Cause 2"},\end{aligned}$$

will indicate how greater is the risk of experiencing a cause among women compared to men.

Chapter 2

EPAMI-D dataset

2.1 General aspects of the dataset

EPAMI-D is a prospective observational study of 286 patients carried out in the Donostia University Hospital. It focuses on a population of patients with acute pancreatitis that represents the most serious population within the spectrum of the AP disease.

Inclusion criteria: patients older than 16 years, admitted to the ICU of Donostia University Hospital with a diagnosis of AP and at least one organ failure. There were no exclusion criteria.

Follow-up: the follow-up time has been set from 1st April 2001 to 31st August 2017. The first individual in the EPAMI-D data entered the 4th of April 2001, whereas the last individual entered the 1st of July 2017. Note that each individual was followed-up since his/her ICU admission until his/her last observed day: either the date of death, or the date of hospital discharge, or the 31st August 2017. See Figure 2.5 and Table 2.2.

Protocol periods: 2001-2007 and 2008-2017: in the last two decades significant changes in the management of AP have taken place. As explained in the Introduction, some practice guidelines have been published in accordance with the advances that have been made. The aim of these protocols is to unify the integral management of potentially severe AP in ICU.

During this study, two treatment protocols have been conducted: one between 2001 and 2007 and other from 2008 to mid-2017. The last protocol encompasses the most recent preferable approaches among intensivists, radiologists, surgeons, gastroenterologists, and other specialists [16].

In very general terms, Table 2.1 presents how the 2008-2017 guideline protocol differs from the 2001-2007 protocol.

2.2 Variables

The following variables were collected at baseline, i.e. at the date of ICU admission, for all 286 patients: age, gender, etiology, body mass index (BMI), intra-abdominal pressure (IAP),

	2001-2007	2008-2017
Detection of severe patients	Criteria to early identify more serious patients and rapidly admit to ICU.	New criteria.
Feeding first 48 hours	Total parenteral feeding established.	If possible, patients should receive enteral feeding.
Antibiotic treatment	Prophylactic antibiotic treatment was prescribed.	There is no indication for use.
Surgery	Immediate open surgery for patients with infected pancreatic necrosis.	If possible, surgery is delayed. The prognosis will be better if the surgery is after 3 weeks of the patient evolution.
Intra-abdominal Pressure (IAP)	Not aware of its importance.	More measurements taken and monitored.

Table 2.1: Some very general differences between 2001-2007 and 2008-2017 protocols

feeding, antibiotics at entry and severity prognostic indices: APACHE II score, SOFA score, Ranson's score and Computed Tomography (CT) severity index.

Pursuing variables were obtained during the course of the disease: ICU entry date, ICU discharge date, pancreatic sepsis, extra-pancreatic sepsis, surgery, date of surgery, use of mechanical ventilation, days under mechanical ventilation, embolisation, date of embolisation, hemodyalisis, days under hemodyalisis, hemorrhage, infected necrosis, ERCP, perforation.

At the end of follow-up the following variables were recorded: classification of severity, death, date of death, cause of death and hospital discharge date.

A more detailed description of these variables is reported in the Appendix A. Severity prognostic indices, such as APACHE II, SOFA, Ranson's score and CT index, are different scoring systems to assess the severity and prognosis of acute pancreatitis. These are predictive methods intended to identify early high-risk patients. Higher values of these scores indicate more severity. While these variables are recorded at baseline, the variable named severity classification is gathered at the end of follow-up. That is, severity classification is computed in the view of the clinical evolution of the patient. It depends on the development or not of organ failure or local complications and is categorized as mild, moderate, severe or critical.

Last, some variables were created. Two of them were: ICU length of stay and total length of stay. The first one accounts for the time period that each patient has spent in the ICU and the latter one refers to the individual follow-up time, i.e. the number of days since the individual ICU admission until the individual last follow-up day. Further, the fulminant variable was created. The patient that did not survive more than two days in ICU was classified as a fulminant patient, since two day survival was not long enough to have a contrast-enhanced computed tomographic scan, nor even to develop 48 hours of acute organ failure. Therefore, in this work a fulminant acute pancreatitis patient was defined as the patient that did not

survive two days (see Appendix A for a stricter clinical definition).

2.3 Complete process of an acute pancreatitis patient

In Figure 2.1 we describe the complete process of an acute pancreatitis patient.

AP is a frequent health problem if one takes into account hospital admissions. The initial symptom of the illness is an acute abdominal pain. In practically all cases, the intensity of this pain forces the patient to go to an emergency service, determining their hospital admission. According to the appearance or not of complications, the episode of acute pancreatitis is classified as: mild, moderate, severe and critical. Approximately in 80% of the patients the inflammation is mild and it usually settles in a few days.

Nevertheless, 15-20% of the cases develop severe disease with associated organ dysfunction and require admission to the ICU. In this unit the mortality could be as high as 30-40%. The individuals that evolve satisfactorily receive the discharge from ICU. Then they might be totally cured and go home, they might enter again to ICU or they might die. Since this is a reversible process —an illness that can be cured— one could relapse and start the described course over again.

EPAMI-D dataset contains the information of the most severe patients, i.e. it only comprises the information of those individuals who entered the ICU, after their arrival to the hospital.

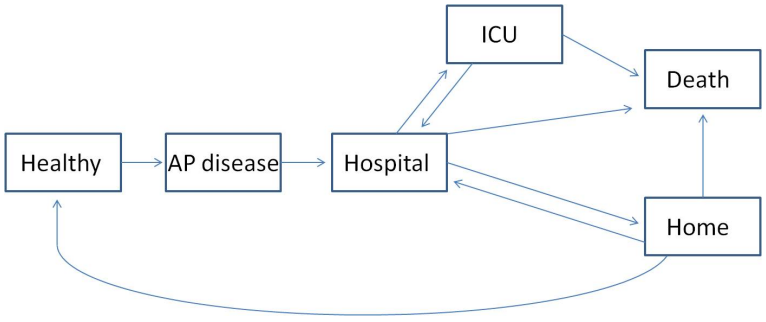


Figure 2.1: States flow diagram of the complete course of patients with AP

2.4 Remark

In the entire EPAMI-D dataset there are different populations to consider. As explained in the Introduction, there is a small group of patients, described as fulminant AP patients, that have a very particular clinical course and should be classified separately. The different management of the patients also divides the dataset into two different populations, see Figure 2.2. Consequently, the analyses should be carried out separately. We place special attention into the individuals that did not happen to be fulminants and that entered during 2008-2017, to whom the second treatment protocol was applied. Actually, the analyses in Chapters 3 and

4 are done using the non-fulminant acute pancreatitis patients of the second treatment group, because the physicians' interest lies in the most recent protocol that they are applying, see the bottom right circle of the Figure 2.2.

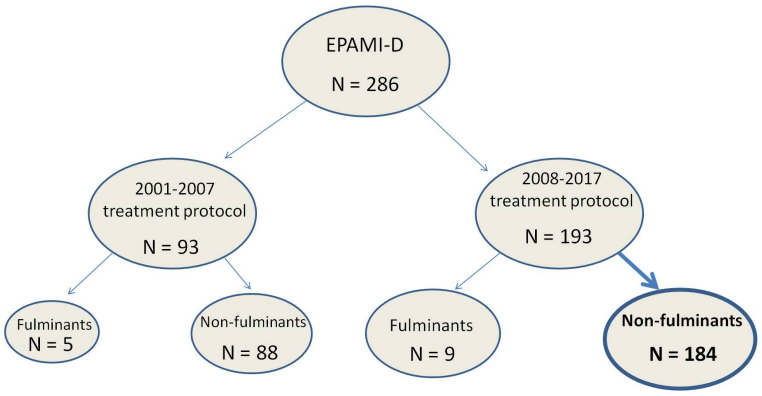


Figure 2.2: Flowchart showing the patients' subgroups in the EPAMI-D dataset

2.5 Descriptive analyses

This section describes the dataset that motivated the work. First of all, we give a general descriptive of the whole EPAMI-D dataset, then, we report the characteristics per treatment protocol group making the distinction between fulminant and non-fulminant acute pancreatitis and finally, we focus on the dataset we analyze in the rest of this project.

2.5.1 General characteristics

General characteristics of the EPAMI-D data are summarized in Table 2.2. Data are described by using the absolute and relative frequencies for categorical variables, mean and standard deviation for continuous variables, or median and interquartile range when is more convenient.

The overall mean age was 59.6 years and 192 (67.1%) patients were male. There were more individuals, 193 (67.5%) patients, in the second treatment protocol group. Concerning the etiology that trigger AP, we observe that biliary lithiasis was the more frequent cause (40.6%) followed by alcohol consumption (22.4%). The mean of APACHE II score was 14 and the mean of CT index 6.7. More about these severity scoring systems can be found in Appendix A. About 173 (60.5%) patients underwent parenteral feeding in the first 48 h, 61 (21.3%) patients had enteral feeding and the rest, 52 (18.2%) of the patients, were not given any artificial nutrition support, either because they did not need it, or because in the cases of fulminant AP patients was not possible to apply any feeding support the first 48 hours.

The median ICU length of stay was 11.5 days (IQR $5 - 24.8$), and the median total length of stay was 33 days (IQR $18 - 67$). Approximately 50% of the follow-up times were less than 33 days. 134 (46.9%) needed surgery and about 166 (58%) required the use of mechanical ventilation.

	Characteristic	Values
Baseline variables	n	286 patients
	Age (yr)	59.6 (± 15.4)
	Gender, n (%)	
	Males	192 (67.1)
	Females	94 (32.9)
	Treatment protocol, n (%)	
	2001-2007	93 (32.5)
	2008-2016	193 (67.5)
	BMI (kg/m^2)	27.3* (± 5.2)
	IAP (mmHg)	18.4** (± 7.1)
	Etiology, n (%)	
	Biliary	116 (40.6)
	Alcoholic	64 (22.4)
	Idiopathic	55 (19.2)
	Others	51 (17.8)
	Severity scores, mean (± sd)	
	APACHE II	14.0 (±6.3)
	SOFA	5.3 (±3.4)
	CT index	6.7(±2.6)
	Ranson's criteria	1.9 (±1.5)
	Feeding, first 48h n (%)	
	Normal	52 (18.2)
	Parenteral	173 (60.5)
	Enteral	61 (21.3)
Time-dependent variables	Local complications, n (%)	
	Infected necrosis	110 (38.5)
	Intestinal perforation	19 (6.6)
	Abdominal hemorrhage	23 (8.0)
	Use of mechanical ventilation, n (%)	166 (58.0)
	Surgery, n (%)	134 (46.9)
	Hemodialysis,n (%)	87 (30.4)
	Embolization, n (%)	16 (5.6)
	ICU LOS, median (IQR)	11.5 (19.8)
	Total LOS, median (IQR)	33.0 (49.0)
Variables at exit (last observation)	Classification n (%)	
	Moderate	71 (24.3)
	Severe	103 (36.0)
	Critical	112 (39.2)
	Fulminant AP patients n (%)	14 (4.9)
	Global mortality n (%)	66 (23.1)
	Mortality causes n (%)	
	Initial systemic inflammatory response syndrome	12 (18.2)
	Local complications	19 (28.8)
	Extrapancreatic infections	5 (7.6)
	Limitation of therapeutical effort (LTE)	23 (34.8)
	Others	7 (10.6)

BMI: Body Mass Index, IAP: Intra-abdominal Pressure, LOS: Length of stay

* 19 missings; ** 175 missings;

Table 2.2: General characteristics of the EPAMI-D dataset patients

The severity forms of these subjects were mostly severe and critical, 103 (36%) and 116 (39.2%) patients respectively. 14 (4.9%) patients had fulminant acute pancreatitis. Overall mortaliy was of 66 (23.1%). From them the most common causes were limitation of therapeutical effort (LTE) and local complications, 23 (34.8%) and 19 (28.8%) cases respectively.

2.5.2 Characteristics per periods of treatment protocol and per fulminant and non-fulminant AP patients

Characteristic	2001-2007 (n= 88)	2008-2017 (n= 184)	Treatment effect (95 % CI)	P-value
Age (yr)	58.1 (± 15.8)	59.6 (± 15.3)	-2.0 (-6.0 to 2.0)	0.437
Gender, n (%)				
Males	58 (65.9)	126 (68.5)	-2.6 (-14.5 to 9.4)	0.672
Females	30 (34.1)	58 (31.5)	2.6 (-9.4 to 14.5)	0.672
BMI (kg/m^2)	27.1* (± 5.7)	27.4** (± 5.0)	-1.0 (-2.0 to 1.0)	0.348
Etiology, n (%)				
Biliary	24 (27.3)	87 (47.3)	-20.0 (-31.8 to -8.2)	**0.002**
Alcoholic	22 (25.0)	40 (21.7)	3.3 (-7.6 to 14.1)	0.549
Idiopathic	23 (26.1)	26 (14.1)	12.0 (1.5 to 22.5)	**0.016**
Others	19 (21.6)	31 (16.9)	4.7 (-5.4 to 14.9)	0.345
Feeding, first 48h n (%)				
Normal	5 (5.7)	36 (19.6)	-13.9 (-21.4 to -6.4)	**0.003**
Parenteral	82 (93.2)	88 (47.8)	45.4 (36.4 to 54.3)	**<0.001**
Enteral	1 (1.1)	60 (32.6)	-31.5 (-38.6 to -24.3)	**<0.001**
Local complications, n (%)				
Infected necrosis	30 (34.1)	76 (41.3)	-7.2 (-19.4 to 5.0)	0.254
Intestinal perforation	5 (5.7)	13 (7.1)	-1.4 (-7.5 to 4.7)	0.668
Abdominal hemorrhage	10 (11.4)	13 (7.1)	4.3 (-3.3 to 11.9)	0.233
Use of mechanical ventilation, n (%)	61 (69.3)	93 (50.5)	18.8 (6.7 to 30.8)	**0.003**
Hemodialysis, n (%)	17 (19.3)	60 (32.6)	-13.3 (-24.0 to -2.6)	**0.023**
Surgery, n (%)	46 (52.3)	83 (45.1)	7.2 (-5.5 to 19.8)	0.268
ICU LOS, median (IQR)	13.5 (21.2)	12 (18)	-	0.580
Total LOS, median (IQR)	38 (41.5)	33 (45.5)	-	**0.007**
Classification n (%)				
Moderate	17 (19.3)	54 (29.3)	-10.0 (-20.6 to 0.5)	0.078
Severe	34 (38.6)	60 (32.6)	6.0 (-6.2 to 18.2)	0.328
Critical	37 (42.0)	70 (38.0)	4.0 (-8.5 to 16.5)	0.527
Global mortality	28 (31.8)	24 (13.0)	18.8 (7.9 to 29.7)	**<0.001**

BMI: Body Mass Index; LOS: Length of stay; * 10 missings; ** 9 missings

Table 2.3: General characteristics of the non-fulminant AP patients according to 2001-2007 or 2008-2017 period of treatment protocol

Regarding non-fulminant AP patients a descriptive comparison of the two periods of treatment with respect to the more relevant variables is given in Table 2.3. Continuous variables are expressed as mean with standard deviation or median and interquartile range. They are compared using Student's t-test, Mann-Whitney test or logrank test. Categorical variables are expressed as absolute numbers and proportions. Pearson's χ^2 test or Fisher's exact test

is used for comparison of categorical variables. A P-value of < 0.05 is considered statistically significant.

Age, BMI and gender did not differ significantly between the two treatment protocol groups, see Table 2.3. Likewise there were no differences between groups regarding local complications, surgery, ICU length of stay and patients severity. In contrast, statistically significant differences were found with regard to the patients etiology. Biliary non-fulminant patients were more frequent in the 2008-2017 period group ($P = 0.002$), while idiopathic non-fulminant AP patients were more predominant in the 2001-2007 group ($P = 0.016$). More enteral feeding is applied in the 2008-2017 treatment protocol group ($P < 0.001$) and there were more patients who did not need nutrition assistance ($P < 0.001$). The parenteral feeding predominate in both groups, 82 (93.2%) and 88 (47.8%) cases respectively, but the use of this was 45.4% higher in the first group than in the second one (P <0.001). There is a significant difference in the use of mechanical ventilation ($P = 0.003$) and hemodialysis ($P = 0.023$). With respect to the total length of stay, the logrank test resulted in a statistically significant difference ($P = 0.007$), non-fulminant AP patients in the 2008-2017 group were under observation of the study less days than the patients in the 2001-2007 group, that is to say, those patients that were applied the second treatment protocol spent less days from their ICU admission until the last observation. Mortality was significantly higher in the 2001-2007 group than in the 2008-2017 group ($P = 0.001$).

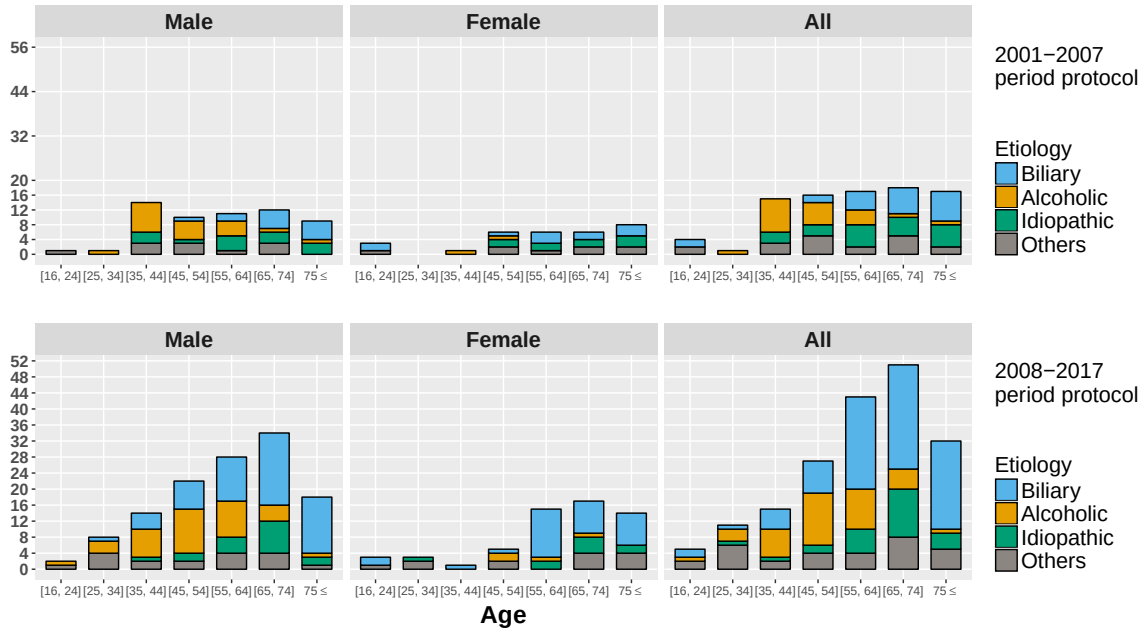


Figure 2.3: Distribution of the non-fulminant AP patients' age in the two treatment protocol groups by gender and etiology

A comparison of the distribution of the age between two treatment protocol groups stratified by gender and etiology is depicted in Figure 2.3. The age distribution is more uniform in the first period group compared to the second one. In the 2008-2017 group, the number of non-fulminant AP patients progressively increases with age. The 65-74 age interval is the one with

more individuals in both men and women. Besides, age and gender distribution differed based on etiology. Alcoholic patients are more common in men. AP in women is more likely related to biliary lithiasis. Overall, regarding age and etiology, biliary lithiasis cases increase with age.

Characteristic	2001-2007 (n= 5)	2008-2017 (n= 9)
Age (yr)	66 (± 15.3)	71.7 (± 5.7)
Gender, n (%)		
Males	3 (60)	5 (55.6)
Females	2 (40)	4 (44.4)
BMI (kg/m^2)	27.2 (± 5.2)	26.6 (± 4.9)
Etiology, n (%)		
Biliary	1 (20)	4 (44.4)
Alcoholic	2 (40)	0 (0)
Idiopathic	2 (40)	4 (44.4)
Others	0 (0)	1 (11.1)

BMI: Body Mass Index;

Table 2.4: General characteristics of the fulminant patients according to 2001-2007 or 2008-2017 period of treatment protocol

5 and 9 fulminant acute pancreatitis cases have occurred in the 2001-2007 and 2008-2017 treatment protocol groups, respectively. There were 3 (60%) men and the mean age was 66 years in the first group, while in the second group were 5 (%55.6) men and the mean age was 71.7 years. Some more details are shown in Table 2.4.

2.5.3 Data to study: further descriptives

Figure 2.5 shows the follow-up time per each patient in the data to study, see bottom right circle of Figure 2.2. Each line goes along the date of the ICU admission of each individual, and it ends in the last observed date: either their hospital discharge, or 31st of August 2017 or date of death, which in this case is indicated by a point. The dotted line corresponds to the ICU length of stay and the solid line to the time since ICU discharge until the last follow-up day. For the sake of clarity, we have set the range of follow-up from 0 to 200 days, although there were two patients with IDs of 116 and 177 —the lines that end with four $\star$— who spent 445 and 233 days respectively from its ICU admission until his/her last follow-up day. Take a look at the illustration of the Figure 2.4 and Table 2.5, for a better comprehension of the Figure 2.5.

The median ICU length of stay was 12 days (IQR $6 - 24$), and the median total length of stay was 33 days (IQR $17.5 - 63$). Approximately 50% of the follow-up times were less than 33 days, see Table 2.2.

A total of 24 (13%) non-fulminant AP patients died during the follow-up in the 2008-2017 treatment protocol, 22 in the Intensive Care Unit and 2 in the hospital once having received their ICU discharge, see the points in Figure 2.5. The most important characteristics related to

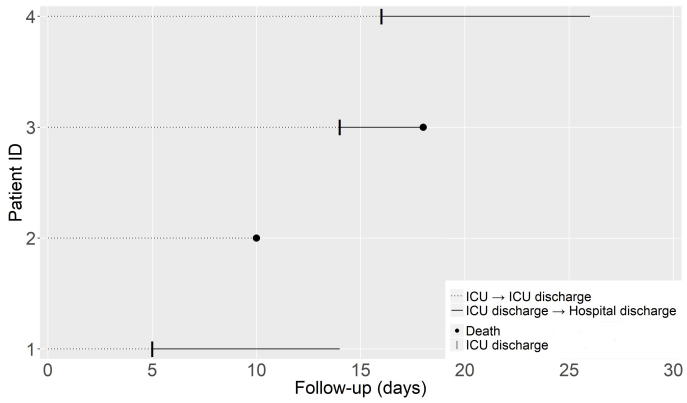


Figure 2.4: Illustration of the follow-up graphic of the Figure 2.5, all the plausible courses

Patient ID	Vital status	ICU LOS	Hospital LOS
4	Alive	16	10
3	Dead	14	4
2	Dead	10	0
1	Alive	5	8

Table 2.5: Description of the Figure 2.4, illustration of the follow-up graphic

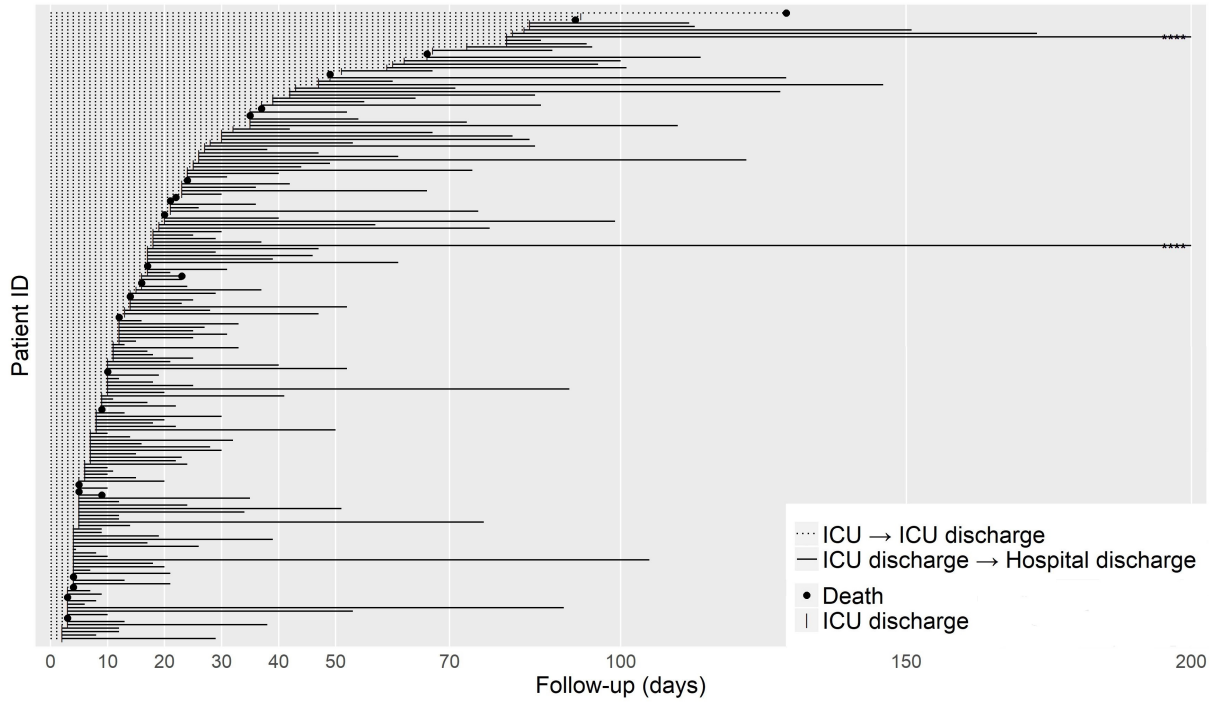


Figure 2.5: Days under the follow-up of the non-fulminant AP patients in the 2008-2017 treatment protocol group of the EPAMI-D data. A point is showed when death and a vertical line when ICU discharge. Dotted line corresponds to the ICU length of stay and the solid line to the time since ICU discharge until the last follow-up day

these patients, as well as the ones related to the whole 2008-2017 period group are summarized in Table 2.6.

With regard to the patients that died during the follow-up, the mean age was approximately of 68 years and 14 (58.3%) were males. The etiology were mostly biliary lithiasis and idiopathic, 10 (41.7%) and 8 (33.3%) individuals respectively. 13 (54.2%) of the patients that

died during the follow-up had the enteral nutrition in the first 48 hours of their ICU admission and 10 (41.6%) went through parenteral. 21 (87.5%) needed mechanical ventilation, 17 (70.8%) hemodialysis and 15 (62.5%) surgery. The median ICU length of stay was 16 days. 15 (62.5%) of these patients developed the critical form of acute pancreatitis.

Respect to the whole group, neither the BMI average nor the gender proportion differed much. The mean APACHE II score was higher in the group of patients that died during the follow-up than in the whole 2008-2017 group, 17.5 and 13.0 respectively. There have been more interventions such as the mechanical ventilation, hemodialysis and surgery in the group of patients that died during the follow-up, and more patients evolved the critical form of acute pancreatitis compared with the enitre 2008-2017 group.

Characteristic	Values	
	Deaths	Total
n	24 patients	184 patients
Age (yr)	68.3 (± 12.6)	59.6(± 15.3)
Gender, n (%)		
Males	14 (58.3)	126 (68.5)
Females	10 (41.7)	58 (31.5)
BMI* (kg/m^2)	27.4 (± 4.8)	27.4 (± 5.0)
Etiology, n (%)		
Biliary	10 (41.7)	87 (47.3)
Alcoholic	3 (12.5)	40 (21.7)
Idiopathic	8 (33.3)	26 (14.1)
Others	3 (12.5)	31 (16.9)
Severity scores, mean (± sd)		
APACHE II	17.5 (±4.0)	13.0 (±5.6)
CT index ⋆	7.2 (±2.6)	7.0(±2.6)
Feeding, first 48h n (%)		
Normal	1 (4.2)	36 (19.6)
Parenteral	10 (41.6)	88 (47.8)
Enteral	13 (54.2)	60 (32.6)
Use of mechanical ventilation, n (%)	21 (87.5)	93 (50.5)
Hemodialysis, n (%)	17 (70.8)	60 (32.6)
Surgery,n (%)	15 (62.5)	83 (45.1)
Embolization, n (%)	0 (0.0)	11 (6.0)
ICU LOS, median (IQR)	16 (22.5)	12 (18)
Classification n (%)		
Moderate	0 (0.0)	54 (29.3)
Severe	9 (37.5)	60 (32.6)
Critical	15 (62.5)	70 (38.0)

BMI: Body Mass Index; * 9 missings; ⋆ 4 missings;

Table 2.6: Some characteristics of the non-fulminant AP patients that passed away in the 2008-2017 treatment protocol

In Figure 2.6, we study the association between the APACHE II severity score, and both, mortality and interventions, in the non-fulminant acute pancreatitis patients of the second 2008-2017 treatment protocol group. In the EPAMI-D dataset APACHE II score ranges from

0 to 34. The higher is the score the more severe is the disease and a higher risk of death is predicted. In view of Figure 2.6, patients who died had been assigned to a higher APACHE II score compared to those who did not die. Besides, the median APACHE II score of the patients undergoing an intervention in the 2008-2017 was higher in contrast with the individuals that were not intervened, specially in the cases of hemodialysis and mechanical ventilation.

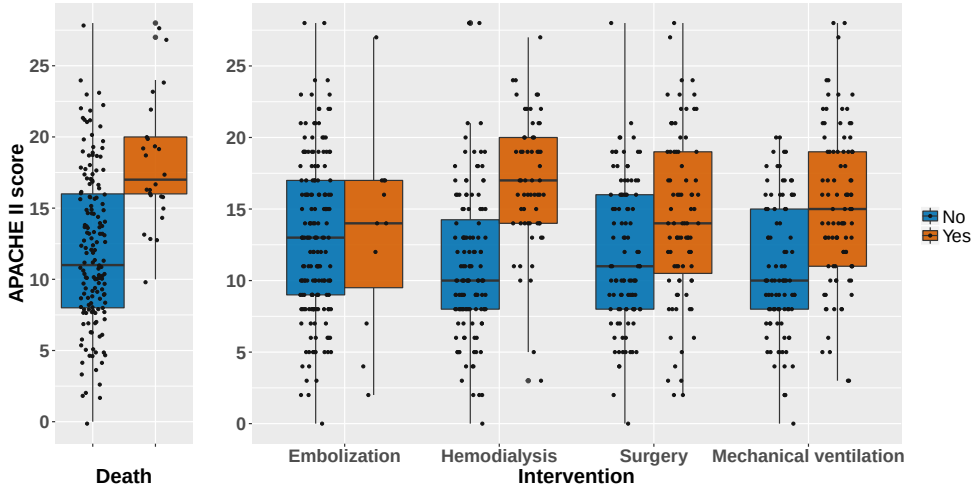


Figure 2.6: Distribution of the death and interventions: embolization, hemodialysis, surgery and mechanical ventilation according to the APACHE II severity scoring system in non-fulminant AP patients of the 2008-2017 period of treatment protocol group

Lastly, since an individual might have had one or more interventions, in Tables 2.7 and 2.8 we measure the association between surgery, and both, mechanical ventilation and hemodialysis.

	Surgery		
Mech. vent.	Yes	No	**Total**
Yes	75	18	93
No	8	83	91
Total	83	101	184

Table 2.7: Contingency table between surgery and mechanical ventilation

	Surgery		
Hemodialysis	Yes	No	**Total**
Yes	44	16	60
No	39	85	124
Total	83	101	184

Table 2.8: Contingency table between surgery and hemodialysis

Hence, we derive that the relative risk of surgery*, $\text{RR}_{\text{S|M}} = \dfrac{P(S|M)}{P(S|\overline{\text{M}})} = \dfrac{75/93}{8/91}$, is 9 times higher among those who underwent through mechanical ventilation than the those who did not. Similarly, the risk of surgery is 2.3, $\text{RR}_{\text{S|H}} = \dfrac{44/60}{39/124}$, higher among the ones who underwent through hemodialysis than the ones who did not.

*S: Surgery
M: Mechacnical ventilation, $\overline{\text{M}}$: no mechanical ventilation
H: Hemodialysis

Chapter 3

The multi-state model

3.1 Proposed multi-state model

We propose the multi-state model illustrated in Figure 3.1. Four states are considered:

State 1: Admission to ICU.

State 2: Discharge (alive) from ICU.

State 3: Death in ICU or in the hospital.

State 4: Discharge (alive) from the hospital.

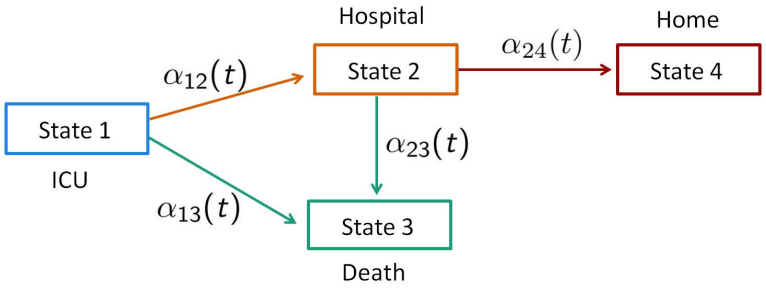


Figure 3.1: Multi-state model for the course non-mild acute pancreatitis

As indicated by the arrows in Figure 3.1, state 1 and 2 are transient states, while 3 and 4 are absorbing states. The arrows indicate as well that only four possible transitions are considered between the four states, that is, a total of five possible histories, see Figure 3.2. In this respect, a patient that is in state 1, ICU, remains in the state "ICU" as long as no other event is observed, i.e. death, or discharge from ICU, or until the end of follow-up. The state 2, "Hospital", is reached when a patient receives the discharge from ICU and the end of the stay in this state is determined by the hospital discharge when the patient is totally cured, by the death or by the end of follow-up. One can arrive to the state 4, "Home", only from the state 2.

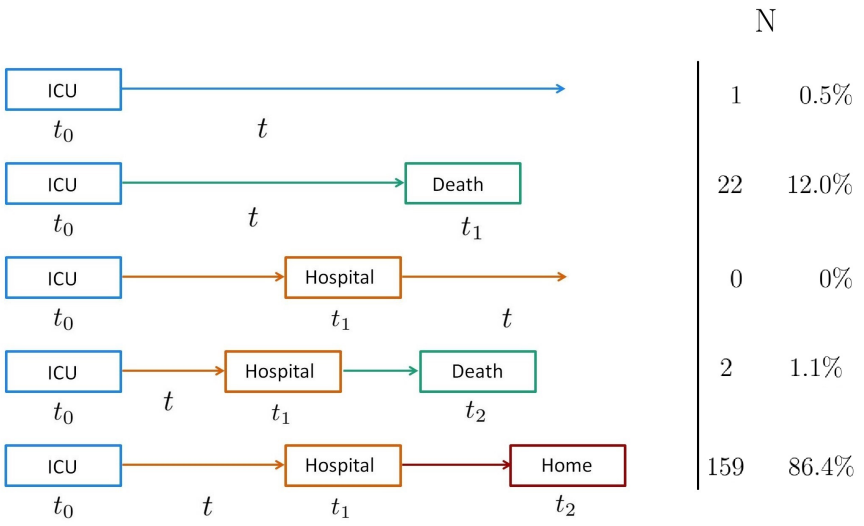


Figure 3.2: All possible trajectories and corresponding number of patients in each trajectory, in the proposed multi-state model

In Table 3.1 we provide the number of patients experiencing each transition. Regarding to this table, a total of 22 (12.0%) patients died in ICU and 161 (87.5%) patients have been discharged from ICU during the follow-up. Among the 161 discharges, 2 (1.2%) patients are known to have died in the hospital and the rest of the patients, 159 (98.8%), received their hospital discharge. At the end of follow-up there is just 1 patient that remained in the ICU and who did not experience any of the events, it is a censored observation.

Transition	No event	Event (%)	Total
ICU → Hospital	23	161 (87.5)	184
ICU → Death	162	22 (12.0)	184
Hospital → Death	159	2 (1.2)	161
Hospital → Home	2	159 (98.8)	161

Table 3.1: Number of patients and number of events in the transitions

3.1.1 Transition probability matrix

The model 3.1 can be described with a 4-by-4 transition matrix, where each entry (l, j) of the matrix represents a possible transition from state l to state j,

$$P(s,t) = \begin{pmatrix} P_{11}(s,t) & P_{12}(s,t) & P_{13}(s,t) & P_{14}(s,t) \\ 0 & P_{22}(s,t) & P_{23}(s,t) & P_{24}(s,t) \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}.$$

We proceed to work out the explicit formulas of the elements of the transition probability matrix. When the model is Markovian we find the transition probabilities as the solution of (1.9). Since state 3 and 4 are absorbing we know that $P_{3,3}(s,t) = 1$ and $P_{4,4}(s,t) = 1$, and since the model is irreversible, we get that $P_{lj}(s,t) = 0$ for all $j > l$.

For the remainder elements we compute equation (1.9),

$$\begin{aligned}\frac{\partial}{\partial t}P_{11}(s,t) &= P_{11}(s,t)(-\alpha_{12}(t) - \alpha_{13}(t) - \alpha_{14}(t)) \\ &= -(\alpha_{12}(t) + \alpha_{13}(t) + \alpha_{14}(t))P_{11}(s,t)\end{aligned}$$

then,

$$\begin{aligned}\frac{\frac{\partial}{\partial t}P_{11}(s,t)}{P_{11}(s,t)} &= -(\alpha_{12}(t) + \alpha_{13}(t) + \alpha_{14}(t)) \\ \frac{\partial}{\partial t}\left(\ln P_{11}(s,t)\right) &= -(\alpha_{12}(t) + \alpha_{13}(t) + \alpha_{14}(t))\end{aligned}$$

we obtain,

$$\begin{aligned}P_{11}(s,t) &= \exp\left(-\int_s^t (\alpha_{12}(u) + \alpha_{13}(u) + \alpha_{14}(u))\mathrm{d}u\right) \\ &= \exp\left\{-\left(A_{12}(s,t) + A_{13}(s,t) + A_{14}(s,t)\right)\right\}.\end{aligned}$$

Similarly,

$$P_{22}(s,t) = \exp\left\{-\left(A_{23}(s,t) + A_{24}(s,t)\right)\right\}.$$

Further,

$$P_{12}(s,t) = \int_s^t \alpha_{12}(u)P_{11}(s,u)P_{22}(u,t)\mathrm{d}u. \tag{3.1}$$

$$P_{23}(s,t) = \int_s^t P_{22}(s,u)\alpha_{23}(u)\mathrm{d}u. \tag{3.2}$$

$$P_{13}(s,t) = \int_s^t \left(\alpha_{13}(u)P_{11}(s,u) + (\alpha_{23}(u))^2 P_{22}(s,u)\right)\mathrm{d}u. \tag{3.3}$$

The steps leading to (3.1)-(3.3) are given in Appendix B.

Now, $P_{14}(s,t) = 1 - P_{11}(s,t) - P_{12}(s,t) - P_{13}(s,t)$ and $P_{24}(s,t) = 1 - P_{22}(s,t) - P_{23}(s,t)$.

3.2 Data format

The data preparation and the multi-state analyses are done using the `mstate` package from **R**, http://CRAN.R-project.org/package=mstate. We show here how the dataset was represented in order to carry out a multi-state analysis in **R**.

First, since the model does not allow patients to enter two states at the same time, we have had to make some small adjustments. If the events of the ICU discharge and the hospital discharge were reported at the same time, we have set the date of the hospital discharge to

be 0.5 day greater. In reality, patients must have been discharged from the ICU before the hospital.

Owing to the fact that the original data was in "wide format", i.e. each row in the data corresponded to a single subject, we have recoded into "long format". So, each subject had as many rows as transitions for which he/she was at risk. A part of the transformed data frame is displayed in Table 3.2, which is a selection of three patients of the EPAMI-D data:

```
An object of class 'msdata'

Data:
    id from to trans Tstart Tstop time status gender age apache age.1 age.2 age.3 age.4
 1  94    1  2     1      0    17   17      1  Mujer  34      9    34     0     0     0
 2  94    1  3     2      0    17   17      0  Mujer  34      9     0    34     0     0
 3  94    2  3     3     17    21    4      0  Mujer  34      9     0     0    34     0
 4  94    2  4     4     17    21    4      1  Mujer  34      9     0     0     0    34
 5  95    1  2     1      0    26   26      1  Mujer  64     11    64     0     0     0
 6  95    1  3     2      0    26   26      0  Mujer  64     11     0    64     0     0
 7  95    2  3     3     26   122   96      0  Mujer  64     11     0     0    64     0
 8  95    2  4     4     26   122   96      1  Mujer  64     11     0     0     0    64
55 109    1  2     1      0    24   24      0 Hombre  48     17    48     0     0     0
56 109    1  3     2      0    24   24      1 Hombre  48     17     0    48     0     0
```

Table 3.2: An extract of the EPAMI-D data in long format

Among others, a variable `trans` was added with a unique value for each possible transition. `Tstart` and `Tstop` corresponds to the starting and leaving time of each entry and state departure, respectively. The time variable `time` equals `Tstart - Tstop`, the time for each transition. Finally, a variable `status` equals 1 if the corresponding transition have occurred, and it has the value 0 otherwise. In the case of a patient that did not experience any event, the time variable was the time until end of follow-up and the `status` variable equals 0 for all transitions for which he/she was at risk.

By means of the `mstate` package, transition specific covariates have been created which are required to study models that assume that the covariates have different effects on each transition. These are derived from the covariates at baseline as follows: each covariate Z is split up into as many covariates Z_{lj} as there are transitions in the model. For the transition from state l to state j, Z_{lj} is equal to Z; for all other transitions, $Z_{lj} = 0$.

Taking a look at Table 3.2, the first subject shown, `id=94`, is firstly at risk for transitions $1 \rightarrow 2$ and $1 \rightarrow 3$. She receives the ICU discharge after 17 days of her entrance to ICU. The transition $1 \rightarrow 3$ (`trans` $= 2$) is censored with 17 as a value. At that moment the patient turns out to be at risk for transition $2 \rightarrow 3$ (`trans` $= 3$) and $2 \rightarrow 4$ (`trans` $= 4$). At 21th day (from the origin) she receives her hospital discharge. The third individual, `id=109`, passes away after 24 days. So the `status` equals 1 for the transition $1 \rightarrow 3$ and he is not longer at risk for a further transition.

3.3 Non-parametric analysis

Before starting to study the covariates' effects in the model via regression models, we carry out a non-parametric analysis.

By means of the Nelson-Aalen estimator of the cumulative transition intensity, $\widehat{\Lambda}_{lj}(t)$ see Equation 1.8, which it is the ratio between the number of $l \to j$ transitions at time t and the number of individuals at risk for the $l \to j$ transtion just before time t, we obtain the results of the Table 3.3. The cumulative hazard functions per each transtion are plotted in Figure 3.3.

	t	$\widehat{A}_{lj}(t)$	$\widehat{\mathrm{Var}}(\widehat{A}_{lj}(t))$		t	$\widehat{A}_{lj}(t)$	$\widehat{\mathrm{Var}}(\widehat{A}_{lj}(t))$
Transition 1→2	2	0.02	0.00	Transition 1→3	2	0.00	0.00
	3	0.07	0.00		3	0.01	0.00
	4	0.17	0.00		4	0.02	0.00
	4.5	0.17	0.00		4.5	0.02	0.00
	...	...	...		...	...	...
	96	3.45	0.23		96	0.69	0.12
	99	3.45	0.23		99	0.69	0.12
	100	3.45	0.23		100	0.69	0.12
	101	3.45	0.23		101	0.69	0.12
	...	...	...		...	...	...
	t	$\widehat{A}_{lj}(t)$	$\widehat{\mathrm{Var}}(\widehat{A}_{lj}(t))$		t	$\widehat{A}_{lj}(t)$	$\widehat{\mathrm{Var}}(\widehat{A}_{lj}(t))$
Transition 2→3	2	0.00	0.00	Transition 2→4	2	0.00	0.00
	3	0.00	0.00		3	0.00	0.00
	4	0.00	0.00		4	0.00	0.00
	4.5	0.00	0.00		4.5	0.03	0.00
	...	...	...		...	...	...
	96	0.04	0.00		96	3.40	0.09
	99	0.04	0.00		99	3.46	0.10
	100	0.04	0.01		100	3.53	0.10
	101	0.04	0.01		101	3.60	0.11
	...	...	...		...	...	...

Table 3.3: A summary of the estimated cumulative hazard intensities and their estimated variances for each of the transitions evaluated at some of the time points for which any event in any transition occurs

The cumulative hazard value depends on the number of events occurred, that is, the function presents a jump whenever a $l \to j$ transition has happened. Provided that, there were 22 events in the ICU $\to$ Death ($1 \to 3$) transition and 2 events in the Hospital $\to$ Death ($2 \to 3$) transition, their corresponding cumulative transition intensities are close to zero. On the other hand, the transitions that correspond to discharges, ICU $\to$ Hospital ($1 \to 2$) and Hospital $\to$ Home ($2 \to 4$) present a sharper increase at the very beginning, due to there have been more early discharges, see Figure 3.3. The increase of the curves becomes steadier as time goes by.

In Chapter 1, we have seen that assuming the model is Markov, it is straightforward to derive the expressions of the transition probabilities as well as their estimations. In fact, in the present chapter we gave the explicit transition probability formulas for our multi-state model and in the Appendix B their estimator's explicit expressions can be found.

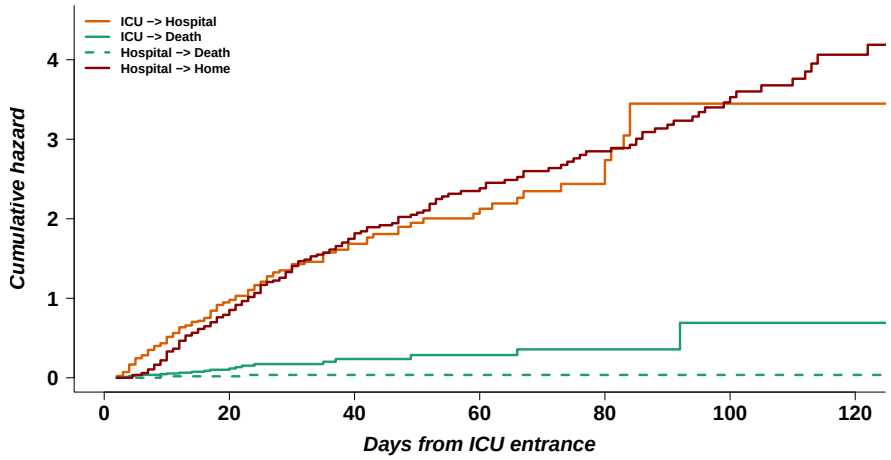


Figure 3.3: Estimated baseline cumulative transition intensities for each of the transitions

Now, one is interested in knowing which are the further probabilities for a patient that has just entered to the Intensive Care Unit, either to remain in the ICU, or receive the discharge from ICU, or die, or receive the discharge from the hospital. For that purpose, we fix the initial time to be $s = 0.5$ and the final time to be $t = 21$ days, after three weeks of the ICU admission. We estimate the following transition intensity matrix and we obtain the following standard errors of each element:

$$\hat{P}(0.5, 21) = \begin{array}{c} \\ \text{I} \\ \text{H} \\ \text{D} \\ \text{Rec.} \end{array} \begin{array}{c} \begin{array}{cccc} \text{I} & \text{H} & \text{D} & \text{Rec.} \end{array} \\ \begin{pmatrix} 0.299 & 0.337 & 0.082 & 0.283 \\ 0 & 0.380 & 0.016 & 0.604 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \end{array} \quad \text{s.e. :} \quad \begin{array}{c} \\ \text{I} \\ \text{H} \\ \text{D} \\ \text{Rec.} \end{array} \begin{array}{c} \begin{array}{cccc} \text{I} & \text{H} & \text{D} & \text{Rec.} \end{array} \\ \begin{pmatrix} 0.032 & 0.035 & 0.019 & 0.034 \\ 0 & 0.050 & 0.015 & 0.050 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array}$$

In consequence, the most probable choice, after three weeks of evolution since the admission to the Intensive Care Unit for a patient with non-mild acute pancreatitis, is to receive the discharge from the ICU, exactly 0.337 (s.e.: 0.035) of probability. The probability of staying in ICU is of 0.299 (0.032), the probability of being totally recovered of 0.283 (0.034), whereas the probability of dying of 0.082 (0.019). Moreover, if at 0.5 day the patient is in the hospital, there is a 0.604 (0.050) probability of recovering, 0.380 (0.050) probability of staying in the hospital and 0.016 (0.015) of dying, after having passed 21 days.

Figure 3.4 plots the first two rows of the previous transition probability matrix. It shows in a clear manner the trends of each transition in the course of time. The dashed line crosses the transition probability curves at the values of the previous transtion probability matrix elements. The left plot corresponds to the first row of the transition probability matrix and the right plot to the second row. Note that on one hand, we have fixed the initial state $l = 1$ ("ICU"), $P_{1j}(0.5, t)$ for all $j = 1, 2, 3, 4$ and $t \geq 0.5$, and on the other hand, $l = 2$ ("Hospital"),

$P_{2j}(0.5, t)$ for all $j = 2, 3, 4$ and $t \geq 0.5$.

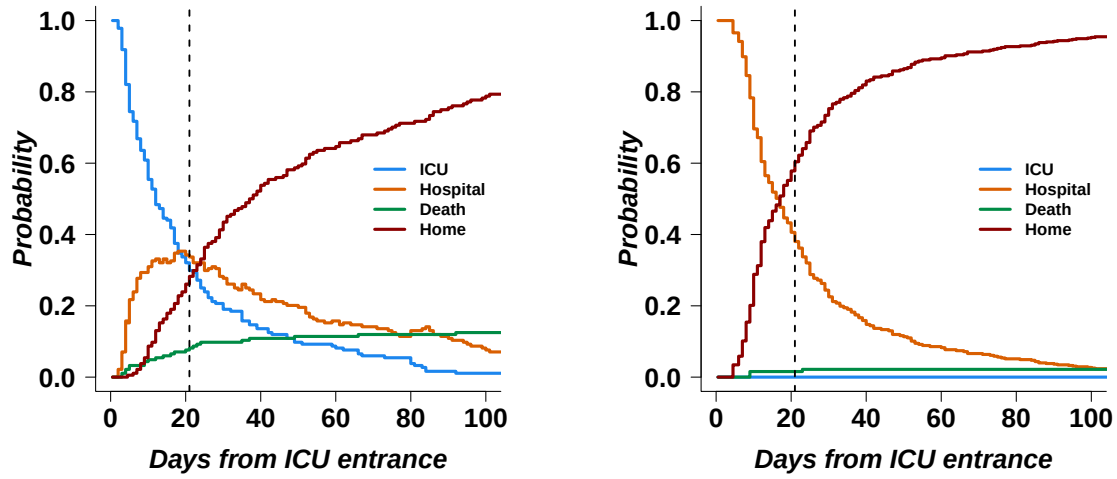


Figure 3.4: Transition probabilities. Left starting in state 1 (ICU) at time 0.5, $P_{1j}(0.5, t)$ for all $j = 1, 2, 3, 4$ and t≥0.5; right starting in state 2 (Hospital) at time 0.5, $P_{2j}(0.5, t)$ for all $j = 2, 3, 4$, and t≥0.5

As seen in Figure 3.4, at time close to 0.5, the only option, in both the left and the right plots, is staying in the initial state, in the ICU or in the hospital respectively, that is, initially the probability of not making any tranisition is 1. As time goes by, this blue curve starts to decrease, at the same time that the other curves start to raise. On the left plot can be observed that the probability of making the ICU → Hospital (1 → 2) transition increases sharply up to the day 20, and that from this day on, the other transitions gain more force. Owing to the fact that the "Death" and the "Home" state are absorbing states their corresponding curves are always monotonously increasing. On the right plot it can be appreciated that the Hospital → Death (2 → 4) transition is almost insignificant, since the green curve does not deviate much from 0. If the patient is in the hospital at 0.5 day, approximately after 18 days on, he/she will have more chance to be fully recovered than staying in the hospital.

Below, in Figure 3.5 we illustrate more transition probability plots, we display the future probabilities for a patient that initially is in state l (fixed) at time s. The above graphics show how the transition probabilities change for patients who still are in the Intensive Care Unit at given times s, and the below graphics show how the transition probabilities change for patients who at given times s are in the hospital. We have chosen 4 initial time points, $s = 0.5, 8, 15$ and 31. Figure 3.6 illustrates equivalently the same transition probability estimates, but here the curves are represented in the commonly used stacked fashion.

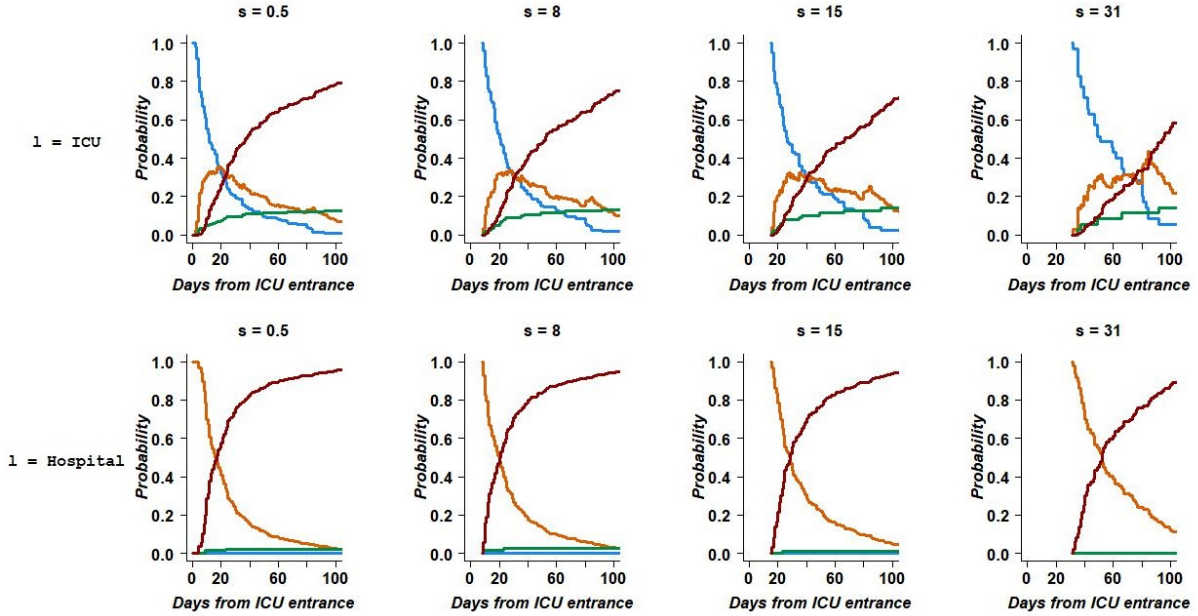


Figure 3.5: Transition probabilities, $P_{lj}(s,t)$. Above starting in state 1 (ICU) at time s, $P_{1j}(s,t)$ for all $j = 1,2,3,4$, $s = 0.5, 8, 15, 31$ and t≥s; below starting in state 2 (Hospital) at time s, $P_{2j}(s,t)$ for all $j = 2,3,4$, $s = 0.5, 8, 15, 31$ and t≥s. The colors of the curves correspond to the final state j, $j = 1$ (ICU, blue), 2 (Hospital, orange), 3 (Death, green) and 4 (Home, red)

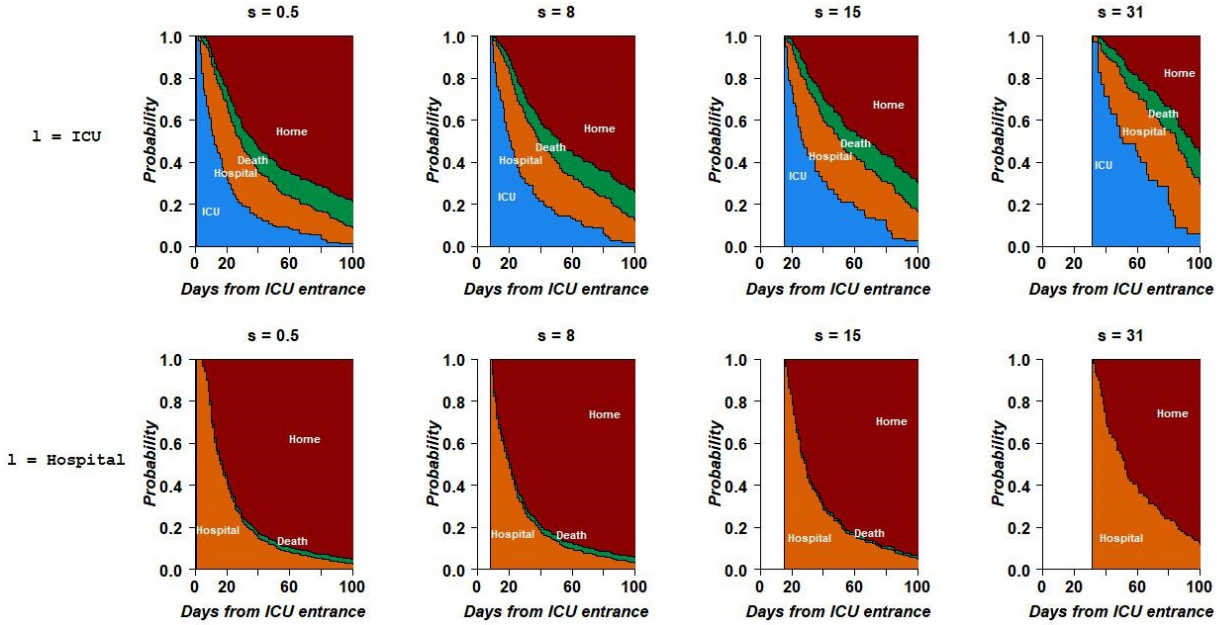


Figure 3.6: Transition probabilities, $P_{lj}(s,t)$ (stacked). Above starting in state 1 (ICU) at time s, $P_{1j}(s,t)$ for all $j = 1,2,3,4$, $s = 0.5, 8, 15, 31$ and t≥s; below starting in state 2 (Hospital) at time s, $P_{2j}(s,t)$ for all $j = 2,3,4$, $s = 0.5, 8, 15, 31$ and t≥s

Chapter 4

Multi-state model analysis

In this chapter we proceed to fit an adequate model for each of the transitions and we focus on the parameter estimation of the most important prognostic factors, for the individuals in the 2008-2017 treatment protocol in the EPAMI-D data.

Due to the great flexibility in modeling the effect of covariates we distinguish two sections. In the first section we introduce the multi-state modelling process and we fit a model that only takes into account baseline covariates. In the second one we extend the analysis considering, along with the previous covariates, one extra time-dependent covariate. This latter model will be more precise and, at the same time, more dynamic. The approach we take is similar to that of Therneau and Grambsch (2001) [21].

4.1 Part I

4.1.1 Three regression models

We fit a separate Cox's proportional hazards model for each of the transitions. Given the baseline covariates Z_m, $m = 1, \ldots, k$, the regression models that we build are:

- **Model for ICU discharge.** A Cox model for the risk to ICU discharge, the model that represents the ICU $\rightarrow$ Hospital $(1 \rightarrow 2)$ transition, is specified by

$$\alpha_{12}(t \mid \mathbf{Z}) = \alpha_{12,0}(t) \exp(\beta_{12,1} Z_1 + \beta_{12,2} Z_2 + \ldots + \beta_{12,k} Z_k),$$

  where $\alpha_{12,0}(t)$ is the baseline transition intensity for ICU discharge.

  The effect measure is given by the hazard ratio,

$$\mathrm{HR}_{12} = \frac{\alpha_{12}(t \mid \mathbf{Z})}{\alpha_{12,0}(t)} = \frac{\alpha_{12}(t \mid \mathbf{Z})}{\alpha_{12}(t \mid \mathbf{Z}_0 = (0, 0, \ldots, 0))} = e^{\beta_{12,1} Z_1 + \beta_{12,2} Z_2 + \ldots + \beta_{12,k} Z_k},$$

  which measures the relative risk of going to the hospital, i.e. receiving the ICU discharge, for a patient with profile $\mathbf{Z}$ compared to a patient with profile $\mathbf{Z}_0 = \mathbf{0}$. We assume that the ratio is constant over time.

- **Model for death.** A Cox model for the risk to death, the model that represents the ICU → Death (1 → 3) transition, is specified by

$$\alpha_{13}(t \mid \mathbf{Z}) = \alpha_{13,0}(t) \exp(\beta_{13,1} Z_1 + \beta_{13,2} Z_2 + \ldots + \beta_{13,k} Z_k),$$

  where $\alpha_{13,0}(t)$ is the baseline transition intensity for death.

  The effect measure is given by the hazard ratio,

$$\mathrm{HR}_{13} = \frac{\alpha_{12}(t \mid \mathbf{Z})}{\alpha_{13,0}(t)} = \frac{\alpha_{13}(t \mid \mathbf{Z})}{\alpha_{13}(t \mid \mathbf{Z}_0 = (0, 0, \ldots, 0))} = e^{\beta_{13,1} Z_1 + \beta_{13,2} Z_2 + \ldots + \beta_{13,k} Z_k},$$

  which measures the relative risk of dying in the ICU for a patient with profile $\mathbf{Z}$ compared to a patient with profile $\mathbf{Z}_0 = \mathbf{0}$. We assume that the ratio is constant over time.

- **Model for recovery.** A Cox model for the risk to hospital discharge, the model that represents the Hospital → Home (2 → 4) transition, is specified by

$$\alpha_{24}(t \mid \mathbf{Z}) = \alpha_{24,0}(t) \exp(\beta_{24,1} Z_1 + \beta_{24,2} Z_2 + \ldots + \beta_{24,k} Z_k),$$

  where $\alpha_{24,0}(t)$ is the baseline transition intensity for the hospital discharge.

  The effect measure is given by the hazard ratio,

$$\mathrm{HR}_{24} = \frac{\alpha_{24}(t \mid \mathbf{Z})}{\alpha_{24,0}(t)} = \frac{\alpha_{24}(t \mid \mathbf{Z})}{\alpha_{24}(t \mid \mathbf{Z}_0 = (0, 0, \ldots, 0))} = e^{\beta_{24,1} Z_1 + \beta_{24,2} Z_2 + \ldots + \beta_{24,k} Z_k},$$

  which measures the relative risk of recovering, i.e. receiving the hospital discharge, for a patient with profile $\mathbf{Z}$ compared to a patient with profile $\mathbf{Z}_0 = \mathbf{0}$. We assume that the ratio is constant over time.

Observation We do not model the transition Hospital → Death (2 → 3), since only two individuals have experienced it.

4.1.2 Assessing the Markov property

We shall check whether the model satisfies the Markov assumption or whether it should be relaxed letting the sojourn times also depend on the times at which earlier states were entered.

That being so, we check for the Hospital → Home (2 → 4) transition if the time at which a patient was discharged from ICU —arrived to the state 2, "Hospital"— influences the subsequent hospital discharge rate, that is, the transition hazard of Hospital → Home (2 → 4). We make use of the transition-specific covariate of `ihtime` for transition 4 (2 → 4), which is `ihtime.4`.

Then, fitting the model,

`ihtime`: a variable that we have created and which accounts for the time that an individual has spent in the Intensive Care Unit

$$\alpha_{24}(t \mid Z_{24,1}) = \alpha_{24,0}(t)\exp(\beta_1 Z_{24,1})$$

where $Z_{24,1}$=`ihtime.4`, β_1 results statistically different from 0 ($P < 0.001$). Consequently, this means that the Hospital $\rightarrow$ Home ($2 \rightarrow 4$) transition hazard depends on the time of arrival at state 2, "Hospital".

In what follows, the Semi-Markov approach or also termed "state arrival extended Markov" model is used for this transition. It is assumed that the sojourn times depend on the history of the process only through the present state and the time since entry of that state.

4.1.3 Obtaining the most appropriate subset of covariates

The next step is to get the most appropriate subset of covariates for the multi-state model. That is, we aim to decide from a set of data which is the subset of covariates that best explain the multi-state model and so we go through comparisons of nested models.

This implies disposing $p+q$ covariates, $Z_1, \ldots, Z_p, Z_{p+1}, \ldots, Z_{p+q}$, and setting two models where the first one has p covariates and the second all of them, i.e. the $p+q$ covariates.

$$\begin{aligned}
&\text{Model 1: } \alpha_{lj}(t \mid \mathbf{Z}) = \alpha_{lj,0}(t)\exp(\beta_{lj,1}Z_1 + \ldots + \beta_{lj,p}Z_p)\\
&\text{Model 2: } \alpha_{lj}(t \mid \mathbf{Z}) = \alpha_{lj,0}(t)\exp(\beta_{lj,1}Z_1 + \ldots + \beta_{lj,p+q}Z_{p+q}).
\end{aligned}$$

The statistical issue is whether the additional q variables improve significantly the explicative power of model 1. The problem can be assessed by formulating the subsequent hypothesis test:

$$\begin{cases} H_0 : \text{Model 1} \\ H_1 : \text{Model 2} \end{cases} \quad \text{or equivalently,} \quad \begin{cases} H_0 : \beta_{lj,p+1} = \beta_{lj,p+2} = \ldots = \beta_{lj,p+q} = 0 \\ H_1 : \exists k \text{ and a } l \rightarrow j \text{ transition that, } \beta_{lj,k} \neq 0 \\ \qquad \text{for } k = p+1, \ldots, p+q. \end{cases}$$

After computing the likelihoods L_1 and L_2 under model 1 and model 2, respectively, we apply the deviance statistic defined as $D_1 - D_2 = -2\log L_1(\hat{\beta}) + 2\log L_2(\hat{\beta}) = -2\log\frac{L_1(\hat{\beta})}{L_2(\hat{\beta})}$, which it is distributed as χ^2_q under H_0. The higher the value of the model's log-likelihood, $L(\hat{\beta_{lj}})$, the better the fit we achieve.

Based on the likelihood ratio test criterion, we select a subset of covariates to incorporate in the model. This is done by an automatic procedure called stepwise analysis. In each step we test the addition of each variable and we add the variable, if any, whose inclusion gives the most statistically significant improvement of the fit. The process is repeated until none improves the model to a statistically significant extent.

In the analysis of this Part I, the potential prognostic factors used were the baseline covariates: age, gender, BMI, etiology, APACHE II and feeding.

We begun building a series of univariate regression models for each possible prognostic factor and we adjusted as well, a model without any variable. The latter was called the null

model in Table 4.1. For each covariate a likelihood ratio test was performed.

$$\text{Null model: } \alpha_{lj}(t \mid \mathbf{Z} = (0, \ldots, 0)) = \alpha_{lj,0}(t)$$
$$\text{Univariate model: } \alpha_{lj}(t \mid \mathbf{Z} = (0, \ldots, Z_m, \ldots, 0)) = \alpha_{lj,0}(t) \exp(\beta_{lj}^T Z_m)$$

The results of these analyses are described in Table 4.1.

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
NONE	1	2896.1			
—	—	—	—	—	—
Age	4	2871.5	24.6	<0.001	2879.5
Gender	4	2891.3	4.8	0.310	2899.3
BMI	4	2891.8	4.3	0.368	2899.8
Etiology	12	2876.7	19.4	0.079	2900.7
APACHE II	4	2849.1	47.0	<0.001	2857.1
Feeding	8	2828.8	67.2	<0.001	2844.8
`ihtime`	2	2877.7	18.4	<0.001	2881.7

Table 4.1: Likelihood ratio tests for each of the seven potential prognostic factors; H_0: null model vs. H_1: univariate model

In the second step we used all covariates that were significant in the univariate analysis at a P <0.25 level. The first variable to include and to continue with the nested comparisons was the one that leaded the highest reduction of the deviance, in this case the feeding variable. Table 4.2 shows the second step in the stepwise regression analysis. In the end, the process resulted in identification, for each of the three events, for a potential set of risk factors. Further outputs are displayed in the Appendix C. The final models for each of the three events were found, using all risk factors that were significant for at least one of the event. Feeding, APACHE II score and age variables were selected. The Table 4.3 reports the final results.

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
Feeding	8	2828.8			2844.8
—	—	—	—	—	—
Feeding + Age	4	2811.1	17.7	0.001	2835.1
Feeding + Etiology	12	2813.4	4.9	0.294	2847.9
Feeding + APACHE II	4	2803.4	25.4	< 0.001	2827.4
Feeding + `ihtime.4`	2	2813.8	15.1	< 0.001	2833.8

Table 4.2: Likelihood ratio tests for H_0: Model 1 (Feeding) vs. H_1: Model 2 (Feeding + Var.)

The transition that studies the chance of a non-mild AP patient being discharged from ICU to hospital, ICU → Hospital (1 → 2) transition, is the transition that showed most significant prognostic factors, see Table 4.3. The hazard of receiving the ICU discharge for a patient

	Variable		Coef.	s.e.(Coef)	HR=exp(Coef.)	CI(HR, 95%)	P-value
$1 \rightarrow 2$ Transition							
	Feeding	Normal					
		Parenteral	-1.396	0.235	0.248	[0.156 - 0.393]	< 0.001
$\beta_{12,m}$		Enteral	-1.447	0.256	0.235	[0.142 - 0.388]	< 0.001
	APACHE II		-0.071	0.017	0.931	[0.902 - 0.962]	< 0.001
	Age		0.003	0.006	1.003	[0.991 - 1.016]	0.618
$1 \rightarrow 3$ Transition							
	Feeding	Normal					
		Parenteral	-0.718	1.120	0.488	[0.054 - 4.378]	0.521
$\beta_{13,m}$		Enteral	-0.360	1.124	0.698	[0.077 - 6.313]	0.748
	APACHE II		0.036	0.048	1.037	[0.944 - 1.139]	0.448
	Age		0.083	0.026	1.086	[1.032 - 1.144]	0.001
$2 \rightarrow 4$ Transition							
	Feeding	Normal					
		Parenteral	-0.345	0.225	0.708	[0.456 - 1.101]	0.126
$\beta_{24,m}$		Enteral	-0.003	0.250	0.997	[0.611 - 1.627]	0.991
	APACHE II		0.009	0.019	1.009	[0.972 - 1.046]	0.646
	Age		-0.006	0.006	0.994	[0.982 - 1.006]	0.320
	`ihtime`		-0.017	0.005	0.983	[0.974 - 0.993]	< 0.001

Table 4.3: Final multi-state model of Part I with all variables selected in the stepwise analysis. Paramter estimates for each transition, standar errors, 95% confidence intervals and p-values

that needed either one of the one forms of nutrition support, parenteral or enteral nutrition, is smaller with respect to a patient that did not need any artificial nutrition support during the first 48 hours of his/her ICU entrance. A patient that did not need any artificial feeding in the first 48 hours have more chance of progressing well and receive the ICU discharge compared to a patient that did need this support. If we revert the coefficients of the parenteral and enteral categories in this way:

$$\begin{aligned} -\beta_{12,1} = 1.396 \quad &\Longrightarrow \quad \mathrm{HR}_{12,1} = \exp(-\beta_{12,1}) = 4.039, \\ -\beta_{12,2} = 1.447 \quad &\Longrightarrow \quad \mathrm{HR}_{12,2} = \exp(-\beta_{12,2}) = 4.250, \end{aligned}$$

the possibility of a patient leaving ICU is greater if he/she did not need any form of nutrition support at the ICU admission, precisely, the hazard is 4.039 times greater with respect to a parenteral and 4.250 times greater with respect to a enteral. The APACHE II score is computed as a result of the several measures made at ICU entrance —such as age, temperature, arterial pressure, heart rate, pH, acute renal failure, respiratory rate, see Appendix A. The greater its value, the more illness severity it indicates. In this case, the effect of the APACHE II score is protective, that is, its hazard ratio is 0.931, less than 1, in this ICU $\rightarrow$ Hospital (1 $\rightarrow$ 2) transition. The risk of evolving satisfactorily in ICU decreases, when the APACHE II score increases, as reasonable. The age variable has not any effect in this transition, the test $H_0 : \beta_{12,4} = 0$ is not statistically significant and the estimate of the hazard ratio is close to 1.

Old age is a well known risk factor for acute pancreatitis mortality. This is also seen in Table 4.3. Regarding ICU $\rightarrow$ Death (1 $\rightarrow$ 3) transition, the only variable from the three selected that resulted statistically significant was age. For instance, if we compare two patients with a difference of 10 years, the hazard ratio is $\mathrm{HR}_{13,4} = \exp(10 * \beta_{13,4}) = \exp(10 * 0.083) = 2.3$. That is, the risk of death is 2.3 times higher for patients that are ten years older. The standard errors are bigger and the corresponding confidence intervals wider due to there were less events, 22 events, in this transition.

The Hospital $\rightarrow$ Home (2 $\rightarrow$ 4) transition measures the chance of being fully recovered, quantifies the chance of being released from the hospital once a patient has passed through the Intensive Care Unit. The selected baseline variables are not statistically significant except the `ihtime.4` variable, the time at which the ICU discharge occurred. Hence, the duration of the ICU stay has a great influence in the recovery process, the less days spent in the Intensive Care Unit, the less days the patient will spend in the hospital. Indeed, the chance of being recovered for a patient that has spent 5 days less in the ICU is $\mathrm{HR}_{24,5} = \exp(-10 * \beta_{24,5}) = \exp(+10 * 0.017) = 1.18$ times greater.

The estimated baseline cumulative transition intensities are plotted in Figure 4.1, they are calculated according to the Equation (1.14) and in Table 4.4 a summary is shown. Notice that these baseline cumulative transition intensities correspond to an individual with profile $\mathbf{Z} = (\text{Normal}, 0, 16)$, i.e. to an individual with covariates "Normal" as the reference category of the feeding variable, APACHE II score equal to 0 and the age equal to the minimum age.

With respect to Figure 4.1, the difference of the three baseline hazards is very noticeable. On one hand, the curves that represent the transition to a desirable recovery state —either

"Hospital" or "Home" state, ICU → Hospital or Hospital → Home transition— are very increasing, meaning that the individuals in the baseline group have great risk of improving and greating well. On the other hand, the risk of dying for the individuals in the baseline group, profile $\mathbf{Z} = (\text{Normal}, 0, 16)$, is very low.

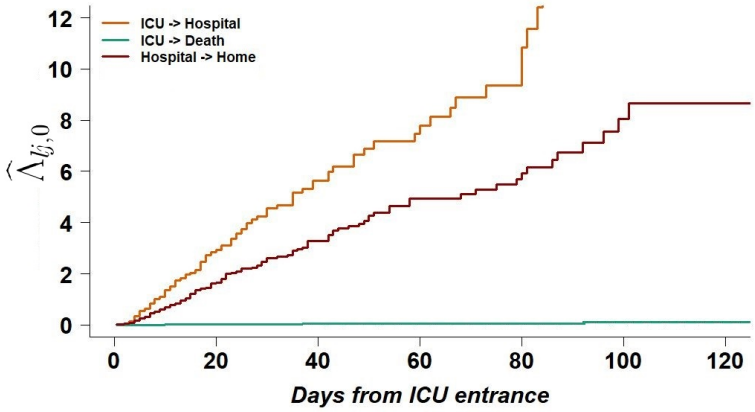


Figure 4.1: Estimated baseline cumulative transition intensities for each of the transitions

	t	$\widehat{A}_{lj}(t)$	$\widehat{\text{Var}}(\widehat{A}_{lj}(t))$		t	$\widehat{A}_{lj}(t)$	$\widehat{\text{Var}}(\widehat{A}_{lj}(t))$
Transition 1→2	0.5	0.00	0.00	Transition 1→3	0.5	0.00	0.00
	2	0.04	0.00		2	0.00	0.00
	3	0.14	0.00		3	0.00	0.00
	4	0.34	0.00		4	0.01	0.00
	...	...	...		...	...	...
	75	9.35	5.93		75	0.06	0.01
	79	9.35	5.93		79	0.06	0.01
	80	10.85	8.18		80	0.06	0.01
	...	...	...		...	...	...
					t	$\widehat{A}_{lj}(t)$	$\widehat{\text{Var}}(\widehat{A}_{lj}(t))$
				Transition 2→4	0.5	0.01	0.00
					2	0.04	0.00
					3	0.09	0.00
					4	0.16	0.00
					...	...	...
					75	5.48	1.86
					79	5.69	2.02
					80	5.92	2.41
					...	...	...

Table 4.4: A summary of the estimated baseline cumulative transition intensities and their estimated variances for each of the transitions evaluated at some of the time points for which any event in any transition occurs

4.2 Part II

The analyses done so far allows one to understand the risk that a patient might have at ICU entrance knowing his/her baseline prognostic factors, i.e. values that are measured or known at this time origin. Further interest will be to update this knowledge and make a more flexible model including one time-dependent variable.

In consideration of the physicians' interest and the information available in the dataset, the surgery variable was chosen as the time-dependent variable to study. In order to model, surgery variable was introduced as the following transition specific covariate for a $l \to j$ transition,

$$D_{lj}(t) = \begin{cases} 0, & \text{if } t < \text{ time of surgery,} \\ 1, & \text{if } t \geq \text{ time of surgery.} \end{cases}$$

For a better understanding of how a time-dependent covariate behaves when incorporated to a Cox model, see Figure 4.2.

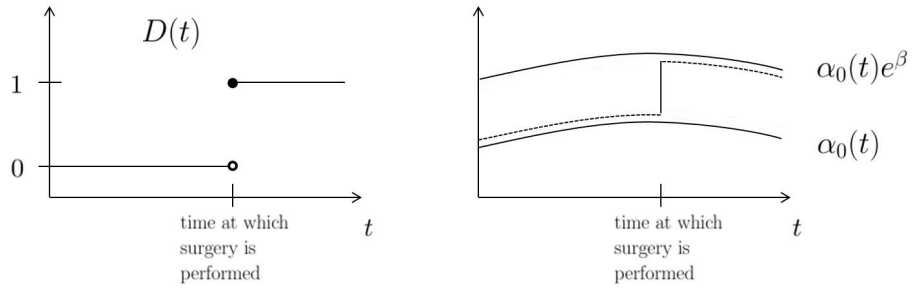


Figure 4.2: Left, an illustration of a time-dependent covariate, $D(t)$. Right, a simple illustration of a Cox model with a time-dependent covariate. The hazard function starts at $\alpha_0(t)$ and "jumps" to $\alpha_0(t)e^{\beta}$ at the moment of $D(t)$, surgery.

4.2.1 Three regression models

Given a set of covariates $\mathbf{Z}(t) = \{Z_1, \ldots, Z_k, D_{12}(t), D_{13}(t), D_{24}(t)\}$, our purpose is to fit the following three regression models:

- **Model for ICU discharge.** A Cox model for the risk to ICU discharge, the model that represents the ICU $\to$ Hospital ($1 \to 2$) transition, is specified by

$$\alpha_{12}(t \mid \mathbf{Z}(t)) = \alpha_{12,0}(t) \exp\{\beta_{12,1}Z_1 + \beta_{12,2}Z_2 + \ldots + \beta_{12,k}Z_k + (\Delta_{12,1}Z_1 + \Delta_{12,2}Z_2 + \ldots + \Delta_{12,k}Z_k)D_{12}(t) + \delta_2 D_{12}(t)\},$$

  where $\alpha_{12,0}(t)$ is the baseline transition intensity for ICU discharge, $\beta_{12,m}$ represents the covariate effects for this transition, δ_2 quantifies the effect of the time-dependent surgery variable and $\Delta_{12,m}$ represents the difference in covariate effects for ICU discharge after

surgery, compared to before surgery. Thus, the sum $\beta_{12,m} + \Delta_{12,m}$ is the total effect for ICU discharge after surgery.

- **Model for death.** A Cox model for the risk to death, the model that represents the ICU $\rightarrow$ Death ($1 \rightarrow 3$) transition, is specified by

$$\alpha_{13}(t \mid \mathbf{Z}(t)) = \alpha_{13,0}(t) \exp\{\beta_{13,1} Z_1 + \beta_{13,2} Z_2 + \ldots + \beta_{13,k} Z_k + (\Delta_{13,1} Z_1 + \Delta_{13,2} Z_2 + \ldots + \Delta_{13,k} Z_k) D_{13}(t) + \delta_3 D_{13}(t)\},$$

where $\alpha_{13,0}(t)$ is the baseline transition intensity for death, $\beta_{13,m}$ represents the covariate effects for this transition, δ_3 quantifies the effect of the time-dependent surgery variable and $\Delta_{13,m}$ represents the difference in covariate effects for death after surgery, compared to before surgery. Thus, the sum $\beta_{13,m} + \Delta_{13,m}$ is the total effect for death after surgery.

- **Model for recovery.** A Cox model for the risk to hospital discharge, the model that represents the Hospital $\rightarrow$ Home ($2 \rightarrow 4$) transition, is specified by

$$\alpha_{24}(t \mid \mathbf{Z}(t)) = \alpha_{24,0}(t) \exp\{\beta_{24,1} Z_1 + \beta_{24,2} Z_2 + \ldots + \beta_{24,k} Z_k + (\Delta_{24,1} Z_1 + \Delta_{24,2} Z_2 + \ldots + \Delta_{24,k} Z_k) D_{24}(t) + \delta_4 D_{24}(t)\},$$

where $\alpha_{24,0}(t)$ is the baseline transition intensity for hospital discharge, $\beta_{24,m}$ represents the covariate effects for this transition, δ_4 quantifies the effect of the time-dependent surgery variable and $\Delta_{24,m}$ represents the difference in covariate effects for hospital discharge after surgery, compared to before surgery. Thus, the sum $\beta_{24,m} + \Delta_{24,m}$ is the total effect for hospital discharge after surgery.

Observation 1 We do not model the transition Hospital $\rightarrow$ Death ($2 \rightarrow 3$), since only two individuals have experienced it.

Observation 2 Note that in the previous models, each of the $l \rightarrow j$ transition intensities depend on whether the patient has undergone surgery ($D_{lj}(t) = 1$) or not ($D_{lj}(t) = 0$), given $Z_1, \ldots, Z_k$:

$$\alpha_{lj}(t \mid D_{lj}(t) = 0) = \alpha_{lj,0}(t) e^{\left\{\beta_{lj,1} Z_1 + \beta_{lj,2} Z_2 + \ldots + \beta_{lj,k} Z_k\right\}},$$
$$\alpha_{lj}(t \mid D_{lj}(t) = 1) = \alpha_{lj,0}(t) e^{\left\{\beta_{lj,1} Z_1 + \beta_{lj,2} Z_2 + \ldots + \beta_{lj,k} Z_k + (\Delta_{lj,1} Z_1 + \Delta_{lj,2} Z_2 + \ldots + \Delta_{lj,k} Z_k) + \delta_j\right\}}.$$

4.2.2 Implementation in R

In **R**, in the `mstate` package, some technical issues might be considered in order to properly carry out the analysis. It has been necessary to intentionally fabricate a "multi-state model", shown in Figure 4.3, so that the estimations including a time-dependent variable were possible.

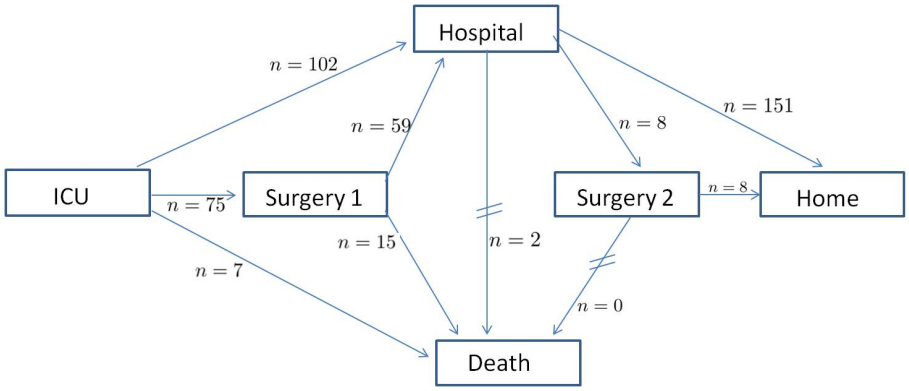


Figure 4.3: The "multi-state model" underneath of the analyses of **R**

After making these arrangements, where we build an augmented dataset, each patient has as many rows as the transitions he/she does, inlcuding two more transitions if the patient has undergone surgery. In this latter case, the first row will correspond to the information just before the surgery and the second one to the information after the surgery.

4.2.3 Estimation

Semi-Markov approach

According to the previous Part I, we perform the analyses using the "state arrival extended Markov" approach. We relax the Markov property and let the transition intensities depend on the time origin $t = 0$ as well as on the time at entry to the present state.

The most appropriate subset of covariates

As explained in section 4.1, we start the model fitting procedure by selecting the most appropriate subset of covariates. In this way, the potential prognostic factors used in the analyses of this Part II were: age, gender, BMI, etiology, APACHE II, feeding and the time-dependent surgery.

Thus in the stepwise regression analysis, we first constructed a series of univariate models for each of the possible prognostic factors and compared them with a null model, see Table 4.5. Afterwards, we identified that the feeding variable was the one that leaded the highest reduction of the deviance. We compared the model with the feeding variable, with seven models that included two and only two variables, the feeding variable and another one of the prognostic factor. Eventually, continuing with the procedure, we come up with the following subset of appropriate covariates: feeding, surgery, APACHE II, BMI and the time to the hospital arrival, `ihtime`. Further outputs of this process are shown in the Appendix C.

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
NONE	1	3736.2			
—	—	—	—	—	—
Age	7	3671.2	65.0	<0.001	3685.2
Gender	7	3714.0	22.2	0.002	3728.0
BMI	7	3682.1	54.1	<0.001	3696.1
Etiology	20	3683.0	53.2	<0.001	3723.0
APACHE II	6	3642.8	93.5	<0.001	3656.8
Feeding	14	3622.3	114.0	<0.001	3650.3
`ihtime`	3	3697.2	39.0	<0.001	3703.2
Surgery	3	3664.6	71.7	<0.001	3670.6

Table 4.5: Likelihood ratio tests for each of the eight potential prognostic factors; H_0: null model vs. H_1: univariate model

Obtaining a more parsimonious model

Once we have done a pre-selection of covariates, we seek to fit a parsimonious model that describes the course of the patients with non-mild AP of the EPAMI-D dataset. Namely, apart from providing an adequate fit to the data, we attempt to obtain a simpler model that is interpretable and explanatory.

We then refit the model leaving out, one by one, those transition-specific covariates that were less significant. The outputs of this process are shown in the Appendix C. On the basis of the results obtained, we arrived to a preferred model which its estimated coefficients, standard errors, confidence intervals and P-values are summarized in Table 4.6.

We note that some covariates had a significant effect on one transition, while for another transition the effect was not apparent. Indeed, some of them were included in a transition, but not in another transition. Also, we obtained different covariate effect estimates across transitions by using transition-specific covariates. One same covariate could have a protective effect for a transition, while a prognostic effect for another transition.

We see in Table 4.6 that the model for ICU discharge provides the following prognostic factors: feeding, APACHE II, surgery and BMI. Herein, parenteral and enteral feeding, as well as APACHE II score, have a protective effect on this transition, i.e. they decrease the risk of being discharged from the Intensive Care Unit. Or if we reverse the coefficients, the interpretation is that a patient who has a low APACHE II score, and/or does not need any nutrition support, will have a higher risk to be discharged from ICU, which is line with the commonly held belief. Reversing the sign of the coefficients, the chance of leaving ICU for a patient that did not need any form of nutrition support is $\exp(-\beta_{12,1}) = 5.56$ greater compared to a patient that needed parenteral nutrition in the first 48 hours, and $\exp(-\beta_{12,2}) = 5.04$ greater compared to a patient that needed enteral nutrition. A decrease of an unit in the APACHE II score implies an increase of 7% for being discharged from ICU. In fact, the hazard ratio is $\exp(-\beta_{12,3}) = 1.07$. Then, if at one point in time the patient had surgery, from that

	Variable		Coef.	s.e.(Coef)	HR=exp(Coef.)	CI(HR, 95%)	P-value
$1 \to 2$ Transition							
$\beta_{12,m}$	Feeding	Normal					
		Parenteral	-1.716	0.265	0.180	[0.107 - 0.302]	< 0.001
		Enteral	-1.617	0.288	0.198	[0.113 - 0.349]	< 0.001
	APACHE II		-0.067	0.020	0.935	[0.900 - 0.973]	< 0.001
δ_2	Surgery		1.953	0.613	7.054	[2.120 - 23.463]	0.001
$\beta_{12,m} + \Delta_{12,m}$	APACHE II		-0.090	0.023	0.914	[0.873 - 0.957]	< 0.001
	BMI		-0.135	0.026	0.874	[0.830 - 0.920]	< 0.001
$1 \to 3$ Transition							
$\beta_{13,m}$	APACHE II		0.159	0.043	1.172	[1.078 - 1.275]	< 0.001
δ_3	Surgery		5.000	0.744	148.471	[34.530 - 638.396]	< 0.001
$2 \to 4$ Transition							
$\beta_{24,m}$	`ihtime`		-0.021	0.005	0.979	[0.970 - 0.988]	< 0.001
δ_4	Surgery		-1.485	0.385	0.226	[0.106 - 0.482]	< 0.001

Table 4.6: Final multi-state model model of Part II with most relevant prognostic factors. Paramter estimates for each transition, standar errors, 95% confidence intervals and p-values

time on the chance of releasing from the Intensive Care Unit increases. From the time that a patient has gone through surgery and onwards, the hazard of this patient being discharged from ICU and go to the hospital is 7.054 times higher compared to a person that has not been intervened. Besides, some interactions arise after this intervention.

Given $\mathbf{Z} = (Z_1, Z_2, Z_3, Z_4, D_{12}(t)) =$ (Parenteral, Enteral, APACHE II, BMI, Surgery), we have:

$$\alpha_{12}(t \mid D_{12}(t) = 0) = \alpha_{12,0}(t)\mathrm{e}^{\{\beta_{12,1}Z_1+\beta_{12,2}Z_2+\beta_{12,3}Z_3\}},$$
$$\alpha_{12}(t \mid D_{12}(t) = 1) = \alpha_{12,0}(t)\mathrm{e}^{\{\beta_{12,1}Z_1+\beta_{12,2}Z_2+(\beta_{12,3}+\Delta_{12,3})Z_3+\Delta_{12,4}Z_4+\delta_2\}}.$$

After the surgery the effect of APACHE II score, measured at the ICU admission, increases. Initially the corresponding hazard ratio is 0.935 and if surgery, the hazard ratio changes to 0.914. That is after surgery, the APACHE II score has a more stronger effect, in the sense that, for the patients who went through surgery the effect of this severity score increases 2.1%. Besides, the body mass index played an important role if surgery have occurred, the corresponding hazard ratio is 0.874. A lower BMI value, if surgery, implies a greater chance to evolve desirably and receive the ICU discharge. The effect of the feeding keeps constant if surgery.

The APACHE II score and surgery have clear effects on the model for death, both are risk factors. The hazard ratio for APACHE II is of 1.196. A difference of 10 points in APACHE II score increases $\exp(10 * 0.159) = 4.9$ times the risk of death. The coefficient estimate of the surgery variable showed a high standard error, s.e.$(\delta_3) = 0.744$, and consequently, wide confidence interval, but we can state that the hazard ratio will be greater than 34, 95% of the time.

In view of the Table 4.6, the factors that mostly explain the recovery model are surgery and the time at which the patient arrived to the hospital once having passed through the ICU, `ihtime`. The hazard ratios are of 0.226 and 0.979, respectively. If surgery or if the time spent in ICU is large, the chance of being recovered decreases. The fact that the hazard ratio of the `ihtime` variable resulted lesser than 1 means somehow that a rapid discharge from the ICU increases the chance of being rapidly recovered.

Goodness of fit

Last, we shall examine the validity of the model and primarily we shall wonder whether the Cox proportional hazards assumption is satisfied. Other aspects, such as the global fit and influential observations, are also important to bear in mind before the model is taken as final, see Appendix C.

To this end, Schoenfeld residuals are useful to check the hazard proportionality hypothesis. Table 4.7 provides the results of the hypothesis tests based on Schoenfeld residuals. The test computes a statistic for each covariate and a global one. Moreover, Figure 4.4 gives a visual insight of the named residuals. Except for the last two variables, $Z_{24,1}$=`ihtime` and

$D_{24}(t)$=Surgery variables, the p-values are higher than 0.05 and we do not reject the null hypothesis, there is not enough statistical evidence to conclude that the proportionality of the covariates is violated. The test for the last two variables resulted to be statistically significant, there are high evidences that the proportionality of the hazards is not satisfied for this covariates.

Covariate	χ^2	P-value
$Z_{12,1}$ = Feeding (Parenteral)	0.28	0.600
$Z_{12,2}$ = Feeding (Enteral)	0.24	0.626
$Z_{12,3}$ = APACHE II	1.24	0.266
$D_{12}(t)$ = Surgery	0.37	0.545
$Z_{12,4}$ = APACHE II	0.00	0.976
$Z_{12,5}$ = BMI	0.24	0.625
$Z_{13,1}$ = APACHE II	0.04	0.842
$D_{13}(t)$ = Surgery	0.14	0.709
$Z_{24,1}$ = `ihtime`	7.91	**0.005**
$D_{24}(t)$ = Surgery	8.09	**0.004**
GLOBAL	8.87	0.544

Table 4.7: Results of the hazard proportionality tests, for each covariate and the global model, by means of the Schoenfeld residuals

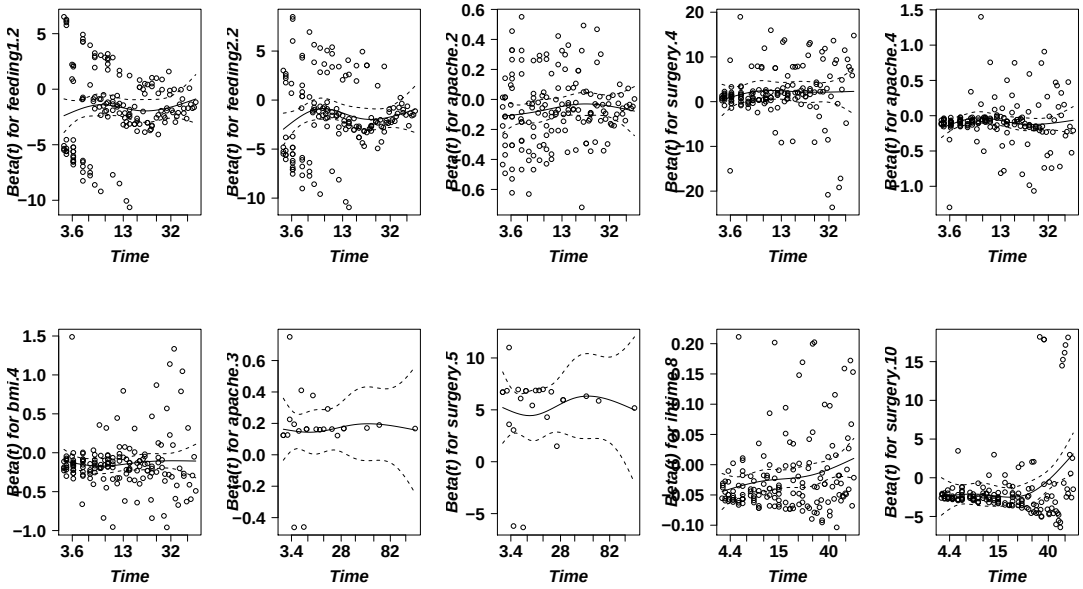


Figure 4.4: Graphical representation of the Schoenfeld residuals for each covariate of the model

We did another check for the variables $Z_{24,1}$=`ihtime` and $D_{24}(t)$=Surgery by means of an analytic method. We first included a variable in the final model $Z_{24,2}(t) = Z_{24,1} * \log(t+1)$ and obtained a p-value equal to 0.510. Next we also fit the final model with the new variable $Z_{24,3}(t) = D_{24}(t) * \log(t+1)$ and we got a p-value equal to 0.986. With the present analytical

checks we do not have many evidences against the proportionality hipothesis of the covariates $Z_{24,1}$=`ihtime` and $D_{24}(t)$=Surgery. Nonetheless, we are aware that there might exist two functions of time, $g_1(t)$ and $g_2(t)$, such that if we included the variables $Z_{24,4}(t) = Z_{24,1} * \log(t+1)$ and $Z_{24,5}(t) = D_{24}(t) * g_2(t)$ in the final model, we would obtain a very low p-value.

Chapter 5

Conclusions

The main aim of this work has been to study the clinical evolution of non-mild acute pancreatitis patients that enter an Intensive Care Unit. To achieve this, we have described the multi-state models from a theoretical point of view, and later on we have attempted to work out the clinical problem on the basis of the multi-state approach. We have proposed a multi-state model and have employed a stratified Cox regression model using the "state arrival extended Markov" approach for inference.

We found, see Table 4.6, that covariates had different effects for different transitions. Most notable result was the effect of surgery in each of the transitions. We estimated high transition rates for surgery, both for the ICU discharge and for the death, although the estimation in the death transition was not as precise enough as one would like to. By contrast, surgery showed a protective effect in the recovery process, Hospital $\rightarrow$ Home ($2 \rightarrow 4$) transition, meaning that a patient who underwent surgery will need more days in order to be fully recovered.

We saw that the time that a patient spent in the Intensive Care Unit had a significant influence on the person's forthcoming course. It resulted that a rapid discharge from the ICU, did help also to a rapid recovery of the patient, i.e. the less time spent in the Intensive Care Unit, the more chances had the patient to recover quickly and receive the hospital discharge in few days.

Regarding the Intensive Care Unit discharge, feeding, APACHE II score and the body mass index, if surgery, were relevant prognostic factors. Patients that needed some type of artificial nutrition support had less chance to be released from the Intensive Care Unit compared to those who did not need any nutrition support. Furthermore, a low APACHE II score, say less severity, helped in the chance of receiving the discharge from the ICU. If surgery happened, the effect of the nutrition was the same, but the effect of APACHE II score changed, as well as the body mass index appeared to have an effect.

The results of the Cox regression model, in Table 4.6, reveal the usual effects of prognostic factors for acute pancreatitis. Although presumably any experienced expert in the field of severe acute pancreatitis is aware, in advance, of these factors, the results might serve as a way of quantifying the risks and obtaining a complete picture of the disease. It is worthwhile to stress that the low incidence and the fluctuating clinical course of the most severe forms of

acute pancreatitis, make the statistical labor to be harder, including the interpretation of the results.

During the study of the EPAMI-D dataset some limitations have arisen. We restricted our analysis from studying the original dataset to studying the patients with non-fulminant acute pancreatitis in the 2008-2017 treatment protocol. The sample size reduction, from 286 to 184, has implied less accurate estimations. We acknowledged that the course of the fulminant AP patients should have been studied adding one extra transition and state, via the multi-state model shown in Figure 5.1.

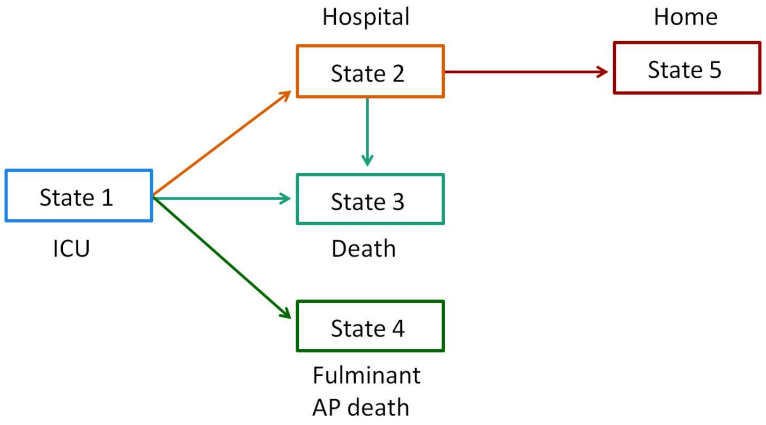


Figure 5.1: An alternative multi-state model for the course non-mild acute pancreatitis which covers the study of the fulminant acute pancreatitis patients

Another aspect to be cautious with is that of confounding bias. For instance, we notice that in the death model the surgery intervention might have been confounded by another factor. We estimated that surgery was a risk factor for the death, a hazard ratio greater than 1, however the effect might not came up because the surgery itself, but because of the degree of severity of the patient. Of course, even if the surgery might be subject to some risks, the variable might be confounded by the fact that patients in a critical situation might very likely have undergone through surgery.

Last, going back to the questions posed in the Introduction, some of them remained open. For instance, it would be interesting to assess the difference between the early surgery and the late surgery and also to obtain predictions of the clinical prognosis of a patient based on the last model. We did not find that the etiology affected the course of acute pancreatitis.

On the whole, we have seen that the multi-state methodology gives a vast insight into the settings where more than one event are of interest. In the EPAMI-D study, particularly, the multi-state approach has been valuable to describe the course of the most severe patients with acute pancreatitis. Besides studying the first event which a patient might have experienced, it has also allowed to describe what happens after this first event. And in this vein, they provide relationship between the different events and the influence of prognostic factors on each of the transition rates.

5.1 Future work

Following we enumerate some points that would be interesting to study further:

- In order to share and communicate the results with the physicians and other experts, it would be very helpful to build an user-friendly shiny application. We believe that this will facilitate the understanding of the methodology.
- Though made in the non-parametric analysis of Chapter 3, we would like to obtain, on the basis of the final model of Part II, individual level predictions. In the end, a main clinical objective is to give prognosis for a patient with a given event-history.
- There exists a wide range of possibilities to study covariate effects in the transition rates other than what we have used in this work. An interesting approach would be to use flexible nonparametric regression models, which are free of some of the assumptions. In particular, Aalen's non-parametric additive model is an attractive alternative. Another common practice is to assume piecewise constant hazards or intensity transitions leading to Poisson regression models.
- I will end mentioning that this work, "A multi-state model for the prognosis of non-mild acute pancreatitis", has been chosen for an oral contribution in the upcoming *XXIXth International Biometric Conference* in Barcelona.

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Appendix A

Clinical summary

A.1 Definitions

- **Body Mass Index (BMI):** the division of the body mass and the square of the body height that is universally expressed in units of kg/m^2. The World Health Organization (WHO) regards a BMI of less than $18.5kg/m^2$ as underweight and may indicate malnutrition, while a BMI equal to or greater than $25kg/m^2$ is considered overweight and above $30kg/m^2$ is considered obese.
- **Intra-abdominal presure (IAP):** the degree of pressure within the abdominal cavity that is expressed in units of mmHg. Elevated IAP is commonly encountered in the critically ill, has detrimental effects on all organ systems, and is associated with significant morbidity and mortality. Normal IAP is approximately 5-7mmHg, IAP in excess of 15mmHg is associated with significant end-organ dysfunction and failure, and an IAP of 20-30mmHg is common in patients with severe sepsis or an acute abdomen.
- **Idiopathy:** any disease with unknown cause or mechanism of apparently spontaneous origin. That is, when the cause may not be readily apparent or characterized.
- **Systematic Inflammatory Response Syndrome (SIRS):** an inflammatory state affecting the whole body, frequently a response of the immune system to infection. The syndrome is a serious condition related to systemic inflammation, organ dysfunction, and organ failure. When SIRS is the result of a confirmed infectious process, it is termed **sepsis**.

  Morbidity and mortality in the first two weeks of AP onset are most commonly associated with the systemic inflammatory response and persistent organ failure rather than local complications. Manifestations of SIRS include, but are not limited to, see table A.1:
- **Limitation of therapeutic effort (LTE):** not to apply extraordinary or disproportionate measures for the therapeutic purpose that arises in a patient with poor vital prognosis and/or poor quality of life. There are two types: not initiating certain measures or withdrawing them when they are in place. This medical term is not free of polemic and a decision of LTE must be based on rigorous criteria.

Finding	Value
Temperature	$< 36°C$ (96.8 ° F) or $> 38°C$ (100.4 ° F)
Heart rate	90/min
Respiratory rate	>20/min or $PaCO_2 < 32$ mmHg (4.3 kPa)
White blood cell count	$< 4 \times 10^9$/L($< 4000/mm^3$), $> 12 \times 10^9$/L($> 12000/mm^3$), or 10% bands

Table A.1: Indications of Systemic inflammatory response syndrome

- **Endoscopic Retrograde Cholangio-Pancreatography (ERCP):** a techinque that combines endoscopy and fluoroscopy to diagnose and treat certain problems of the biliary or pancreatic ductal systems. Through the endoscope, the physician see the inside of the stomach and duodenum, and inject a contrast medium, which is a substance used to enhance the visibility of blood vessels and the gastrointestinal tract in medical imaging, into the ducts in the biliary tree and pancreas so they can be seen on radiographs.

- **Parenteral nutrition (PN):** the feeding of a person intravenously, bypassing the usual process of eating and digestion which is provided when the gastrointestinal tract is non-functional because of an interruption in its continuity or because its absorptive capacity is impaired.

- **Enteral nutrition (EN):** the provision of nutrients through the gastrointestinal tract when the patient cannot ingest, chew, or swallow food, but can digest and absorb nutrients. Methods of administration include oral, sublingual (dissolving the drug under the tongue), and rectal. This feeding is usually preferable to parenteral since it is less prone to complications.

- **Necrosis:** the morphological pattern of pathological death of a set of cells or any tissue in a living organism, caused by a harmful agent that causes a so serious lesion that it cannot be repaired or cured.

- **Mechanical ventilation:** artificial ventilation where mechanical means are used to assist or replace spontaneous breathing. It is termed "invasive" if it involves any instrument penetrating through the mouth, e.g. an endotracheal tube, or the skin, e.g. a tracheostomy tube. Mechanical ventilation is instituted to correct blood gases and reduce the work of breathing, either it is indicated when the patient's spontaneous ventilation is inadequate to maintain life.

- **Hemodialysis:** a process of purifying the blood of a person whose kidneys are not working normally. This type of dialysis achieves the extracorporeal removal of waste products such as creatinine, urea and free water from the blood when the kidneys are in a state of kidney failure. It is one of three renal replacement therapies along with kidney transplant and peritoneal dialysis.

- **Gastrointestinal perforation:** a hole in the wall of part of the gastrointestinal tract. It typically requires emergency surgery and it is usually carried out along with intravenous fluids and antibiotics.
- **Embolisation:** the passage and lodging of an embolus within the bloodstream. It may be pathological, for example a pulmonary embolism, or therapeutic, as a hemostatic treatment for bleeding or as a treatment for some types of cancer by deliberately blocking blood vessels to starve the tumor cells.
- **Fulminant acute pancreatitis:** defined by either single grade 2-3 organ failure or 2≥ organ failures developed within 72 hours of onset of acute pancreatitis.

A.2 Systems for scoring severity of AP

Severity scoring systems are used in conjunction with other risk factors, e.g. disease etiology, to anticipate and estimate outcomes such as ICU mortality. The scores are meant to assess the severity and prognosis of acute pancreatitis.

The rationale for using scoring systems in a clinical environment is to ensure that the increased complexity of disease in patients currently being treated is consistently represented for all those involved in the form of evaluations and descriptions.

Nevertheless, the goal of severity scoring can be more than just obtaining a figure representing the degree of physiological disturbance. Distinguishing the AP categories enables the classification of patients into homogeneous severity groups, in which the duration of hospitalisation and the treatment varies. For instance, severe pancreatitis will need intensive care therapy whereas mild pancreatitis can be treated on the common ward. So, the scores serve as a pretreatment protocol and as a tool with which clinicians could more accurately monitor patients and implement the use of new therapies.

What follows is a summary description of some of the scoring systems currently in use in medical procedure.

- **Ranson criteria:** one of the first scoring systems used to assess prognosis in AP. It consists of 11 parameters, 5 assessed at admission and 6 more during the next 48 hours

  Ranson at admission ranges from 0 to 5 and at 48 hours ranges from 0 to 6. A score ≥ 3 is interpreted as a severe AP.
- **Balthazar Computed Tomography Severity index, CT index:** based on findings from a Computed Tomography (CT) scan with intravenous contrast to assess the severity of AP. It is accepted as the imaging procedure of choice: first to document the extent of pancreatic and extrapancreatic acute fluid collections and, second, to detect pancreatic necrosis. CT index is based on the sum of:
  - Balthazar score: grading of pancreatitis (A-E), that is, presence of collections.
  - Grading the extent of pancreatic necrosis

It ranges from 0 to 10 and is usually classified as:

  - 0-3: mild AP
  - 4-6 moderate AP
  - 7-10 severe AP

- **Acute Physiology and Chronic Health Evaluation II, APACHE II:** computed on the basis of 14 measurements, 12 physiological variables and 2 disease-related variables, that are calculated at the beginning of the ICU admission to help determine the patients mortality risk for the admission. It is an integer score that ranges from 0 to 71 where higher scores imply a more severe disease and, therefore, a higher risk of death.

  It is used extensively in clinical practice due to its simplicity of calculation and the abundance of related medical documentation.

- **Sequential Organ Failure Assessment, SOFA:** based on six different scores, one each for: respiratory (inspiration air pressure), coagulation (platelet count), hepatic (liver, bilirrubine), cardiovascular (hypotension), neurological (Glasgow Coma score) and renal (creatinine or urine output) systems. The scoring for each system ranges from 0 for "normal function" to 4 for "maximum failure/dysfunction". The final SOFA score is the addition of the dysfunction indexes for all organs/systems. The maximum possible SOFA score is 24, corresponding to maximum failure for all of the six organs/systems considered.

  When combined with additional parameters, it provides a set of features for outcome assessment and also for the study of the evolution of sepsis into its more severe states.

A.3 Classification of the AP severity at the end of the course

At the end of the course, physicians classify each patient AP severity degree in the view of their clinical evolution. The objective of this classification is to order cases, compare results between different centers and to avoid inclusion biases. In contrast, the objective of the initially calculated AP severity scores is to predict the prognosis.

In the EPAMI-D dataset Determinant-Based Classification is used which includes four grades: mild, moderate, severe and critical. The classification depends on the development or not of organ failure or local complications, see Table A.2.

Severity Category	**Local Determinant**		**Systemic Determinant**
Mild	No local complications	*and*	No organ failure
Moderate	Sterile pancreatic and peripancreatic complications	*or*	Transient organ failure
Severe	Infectious pancreatic and peripancreatic complications	*or*	Persistent organ failure
Critical	Infectious pancreatic and peripancreatic complications	*and*	Persistent organ failure

Table A.2: Determinant-Based Classification of acute pancreatitis

Appendix B

Some calculations

B.1 Variance estimates for cumulative transition hazard estimator

- Aalen:

$$\widehat{\mathrm{Var}}(\widehat{A}_{lj}(t)) = \sum_{s \leq t} \frac{\Delta N_{lj}(s)}{Y_l^2(s)}, \quad \text{for } l, j \in \mathcal{S} \text{ and if } l \neq j. \tag{B.1}$$

- Greenwood:

$$\widehat{\mathrm{Var}}(\widehat{A}_{lj}(t)) = \sum_{s \leq t} \frac{\Delta N_{lj}(s)}{Y_l(s)(Y_l(s)-1)}, \quad \text{for } l, j \in \mathcal{S} \text{ and if } l \neq j. \tag{B.2}$$

B.2 Explicit formulas for transition probabilities

We derive $P_{12}(s,t)$,

$$\begin{aligned}\frac{\partial}{\partial t} P_{12}(s,t) &= P_{11}(s,t)\alpha_{12}(t) + P_{12}(s,t)(-\alpha_{23}(t) - \alpha_{24}(t)) \\ &= \alpha_{12}(t)P_{11}(s,t) - (\alpha_{23}(t) + \alpha_{24}(t))P_{12}(s,t).\end{aligned}$$

$$\frac{\partial}{\partial t} P_{12}(s,t) + (\alpha_{23}(t) + \alpha_{24}(t))P_{12}(s,t) = \alpha_{12}(t)P_{11}(s,t)$$

$$\frac{\partial}{\partial t} P_{12}(s,t) \exp\left(\int_s^t (\alpha_{23}(u) + \alpha_{24}(u))du\right) + (\alpha_{23}(t) + \alpha_{24}(t))P_{12}(s,t) \exp\left(\int_s^t (\alpha_{23}(u) + \alpha_{24}(u))du\right) = \alpha_{12}(t)P_{11}(s,t) \exp\left(\int_s^t (\alpha_{23}(u) + \alpha_{24}(u))du\right)$$

Recognizing the left-hand side as a partial derivative we have,

$$\frac{\partial}{\partial t}\left[P_{12}(s,t) \exp\left(\int_s^t (\alpha_{23}(u) + \alpha_{24}(u))du\right)\right] = \alpha_{12}(t)P_{11}(s,t) \exp\left(\int_s^t (\alpha_{23}(u) + \alpha_{24}(u))du\right).$$

Therefore,

$$P_{12}(s,t)\exp\left(\int_s^t(\alpha_{23}(u)+\alpha_{24}(u))du\right)=\int_s^t\alpha_{12}(u)P_{11}(s,u)\exp\left(\int_s^u(\alpha_{23}(v)+\alpha_{24}(v))dv\right)\mathrm{d}u,$$

$$\begin{aligned}P_{12}(s,t)&=\exp\left(-\int_s^t(\alpha_{23}(u)+\alpha_{24}(u))du\right)\int_s^t\alpha_{12}(u)P_{11}(s,u)\exp\left(\int_s^u(\alpha_{23}(v)+\alpha_{24}(v))dv\right)\mathrm{d}u\\&=\int_s^t\alpha_{12}(u)P_{11}(s,u)\exp\left(\int_u^t(\alpha_{23}(v)+\alpha_{24}(v))dv\right)\mathrm{d}u\\&=\int_s^t\alpha_{12}(u)P_{11}(s,u)P_{22}(u,t)\mathrm{d}u.\end{aligned}\tag{3.1}$$

The probability $P_{23}(s,t)$,

$$\begin{aligned}\frac{\partial}{\partial t}P_{23}(s,t)&=P_{22}(s,t)\alpha_{23}(t)\\P_{23}(s,t)&=\int_s^t P_{22}(s,u)\alpha_{23}(u)\mathrm{d}u.\end{aligned}\tag{3.2}$$

For $P_{13}(s,t)$,

$$\begin{aligned}\frac{\partial}{\partial t}P_{13}(s,t)&=P_{11}(s,t)\alpha_{13}(t)+P_{23}(s,u)\alpha_{23}(t),\\P_{13}(s,t)&=\int_s^t\left(\alpha_{13}(u)P_{11}(s,u)+\alpha_{23}(u)P_{23}(s,u)\right)\mathrm{d}u\\&=\int_s^t\left(\alpha_{13}(u)P_{11}(s,u)+(\alpha_{23}(u))^2P_{22}(s,u)\right)\mathrm{d}u\end{aligned}\tag{3.3}$$

B.3 Estimations

$$\widehat{P}_{11}(s,t)=\prod_{s<u\le t}\left(1-\mathrm{d}\widehat{A}_{12}(u)-\mathrm{d}\widehat{A}_{13}(u)-\mathrm{d}\widehat{A}_{14}(u)\right)\tag{B.3}$$

$$\widehat{P}_{22}(s,t)=\prod_{s<u\le t}\left(1-\mathrm{d}\widehat{A}_{23}(u)-\mathrm{d}\widehat{A}_{24}(u)\right)\tag{B.4}$$

$$\widehat{P}_{12}(s,t)=\sum_{s<u\le t}\widehat{P}_{11}(s,u^-)\mathrm{d}\widehat{A}_{12}(u)\widehat{P}_{22}(u^+,t)\tag{B.5}$$

$$\widehat{P}_{23}(s,t)=\sum_{s<u\le t}\mathrm{d}\widehat{A}_{23}(u)\widehat{P}_{22}(s,u^-)\tag{B.6}$$

$$\widehat{P}_{13}(s,t)=\sum_{s<u\le t}\left(\mathrm{d}\widehat{A}_{13}(u)\widehat{P}_{11}(s,u^-)+\mathrm{d}\widehat{A}_{23}(u)\right)^2\widehat{P}_{22}(s,u^-)\tag{B.7}$$

$$\begin{aligned}\widehat{P}_{14}(s,t)=&\sum_{s<u\le t}\widehat{P}_{11}(s,u^-)\mathrm{d}\widehat{A}_{12}(u)\widehat{P}_{22}(u^+,t)+\sum_{s<u\le t}\widehat{P}_{11}(s,u^-)\mathrm{d}\widehat{A}_{13}(u)\\&+\sum_{s<u\le t}\widehat{P}_{11}(s,u^-)\mathrm{d}\widehat{A}_{14}(u)\end{aligned}\tag{B.8}$$

$$\widehat{P}_{24}(s,t)=\sum_{s<u\le t}\widehat{P}_{22}(s,u^-)\mathrm{d}\widehat{A}_{23}(u)+\sum_{s<u\le t}\widehat{P}_{22}(s,u^-)\mathrm{d}\widehat{A}_{24}(u)\tag{B.9}$$

Appendix C

Further analyses

C.1 Tables of stepwise analysis results, Part I

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
Feeding + APACHE II	4	2803.4			2827.4
—	—	—	—	—	—
Feeding + APACHE II + Age	4	2787.7	15.6	0.004	2819.7
Feeding + APACHE II + Etiology	12	2788.2	15.2	0.233	2836.2
Feeding + APACHE II + `ihtime.4`	2	2788.1	15.2	< 0.001	2816.1

Table C.1: Likelihood ratio tests for H_0: Model 1 (Feeding + APACHE II) vs. H_1: Model 2 (Feeding + APACHE II + Var.)

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
Feeding + APACHE II + Age	3	2864.3			2888.3
—	—	—	—	—	—
Feeding + APACHE II + Age + Etiology	9	2848.5	15.8	0.071	2890.5
Feeding + APACHE II + Age+ `ihtime.4`	1	2851.3	12.9	< 0.001	2877.3

Table C.2: Likelihood ratio tests for H_0: Model 1 (Feeding + APACHE II + Age) vs. H_1: Model 2 (Feeding + APACHE II + Age + Var.)

C.2 Tables of stepwise analysis results, Part II

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
Feeding	12	3622.3			3650.3
—	—	—	—	—	—
Feeding + Age	7	3602.2	20.1	0.005	3644.2
Feeding + Gender	7	3613.5	8.7	0.272	3655.5
Feeding + BMI	7	3609.5	12.7	0.078	3651.5
Feeding + Etiology	20	3596.2	26.1	0.164	3644.2
Feeding + APACHE II	7	3583.7	38.6	<0.001	3625.7
Feeding + `ihtime`	3	3598.6	23.7	<0.001	3632.6
Feeding + Surgery	3	3571.8	50.5	<0.001	3603.8

Table C.3: Likelihood ratio tests; H_0: Model 1 (Feeding) vs. H_1: Model 2 (Feeding + Var.)

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
Feeding + Surgery	3	3571.8			3603.8
—	—	—	—	—	—
Feeding + Surgery + Age	7	3564.6	13.3	0.065	3602.5
Feeding + Surgery + gender	7	3571.3	6.5	0.485	3609.3
Feeding + Surgery + BMI	7	3543.2	34.6	<0.001	3581.2
Feeding + Surgery + Etiology	20	3554.0	23.8	0.252	3618.0
Feeding + Surgery + APACHE II	7	3536.8	41.0	<0.001	3574.8
Feeding + Surgery + `ihtime`	3	3556.7	21.1	<0.001	3586.7

Table C.4: Likelihood ratio tests; H_0: Model 1 (Feeding + Surg.) vs. H_1: Model 2 (Feeding + Surg. + Var.)

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
Feeding + Surgery + APACHE II	7	3536.8			3574.8
—	—	—	—	—	—
Feeding + Surgery + APACHE II + Age	7	3529.8	7.0	0.430	3581.8
Feeding + Surgery +APACHE II + gender	7	3531.9	4.9	0.670	3583.9
Feeding + Surgery + APACHE II + BMI	7	3520.3	16.5	0.021	3572.3
Feeding + Surgery + APACHE II + Etiology	20	3514.9	21.9	0.345	3592.9
Feeding + Surgery + APACHE II + `ihtime`	3	3515.2	21.6	<0.001	3559.2

Table C.5: Likelihood ratio tests; H_0: Model 1 (Feeding + Surg. + APACHE II) vs. H_1: Model 2 (Feeding + Surg. + APACHE II + Var.)

Variables	Df	-2 log$L_1(\hat{\beta})$	χ^2	p-value	AIC
Feeding + Surgery + APACHE II + `ihtime`	3	3515.2			3559.2
—	—	—	—	—	—
Feeding + Surgery + APACHE II + `ihtime` + age	7	3508.2	7.4	0.393	3565.8
Feeding + Surgery +APACHE II + `ihtime` + gender	7	3508.2	7.0	0.426	3566.2
Feeding + Surgery + APACHE II + `ihtime` + BMI	7	3500.4	14.8	0.039	3552.4
Feeding + Surgery + APACHE II + `ihtime` + Etiology*	20	-	-	-	-

* convergence problem

Table C.6: Likelihood ratio tests; H_0: Model 1 (Feeding + Surg. + APACHE II + BMI) vs. H_1: Model 2 (Feeding + Surg. + APACHE II + BMI + Var.)

C.3 Obtaining a more parsimonious model, Part II

We have used a stepwise selection, but unlike in the previous section, we begin with a model with all 5 variables (variables chosen in the previous B.2). This is called backward stepwise selection: remove the variable with the largest p-value, that is, the variable that is the least statistically significant. Then, fit a new model with 5-1 variables, and test this model with the model with all variables. We continue until arriving to a model that does not need to remove any variable because its explicative power can not be improved more.

C.4 Verifying the final model, Part II

Verification of the global fit by means of the Cox-Snell residuals, see Figure C.1.

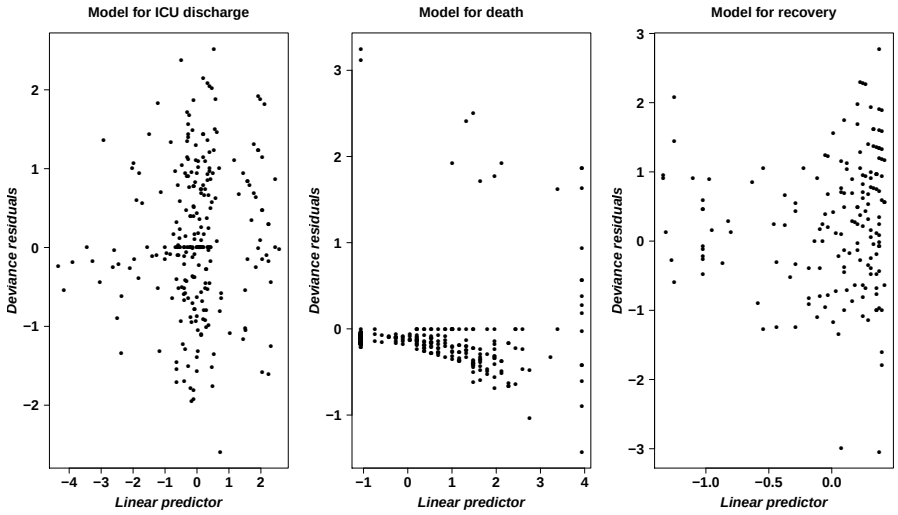

Figure C.1: Cox-Snell residuals to check the global fit

Influence of each individual in the global fit using `dfbeta` residuals, which are residuals based on the transformed *scores*. Each residual approximate the change in the coefficient vector if that observation were dropped, see Figure C.2.

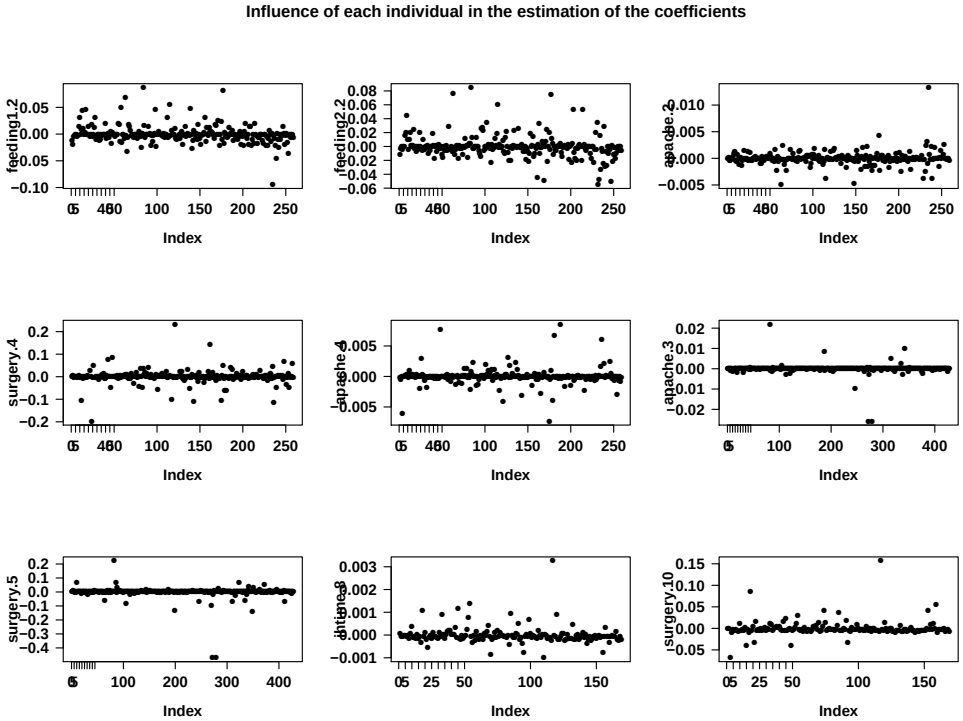

Figure C.2: `dfbeta` residuals to determine the influence of each individual in the estimation of the coefficients

Appendix D

R code

In the following, we describe the implemented code in order to carry out the analysis in **R** (R Development Core Team, 2016). Three packages were needed: `survival` [23], `mstate` [24] and `ggplot2` [25].

D.1 Descriptive analyses

For descriptive analysis we created these functions so as to we entered as the argument the dataset and obtain the results automatically per each feature of the data.

```
resumen <- function(df, ...) {
  require(descr)
  cats <- which(sapply(df, function(x) is.factor(x) | is.character(x)))
  nums <- which(sapply(df, is.numeric))
  if (length(cats) > 0) {
    catxt <- '\nDescription of categorical variables'
    cat(catxt, '\n')
    cat(rep('=', nchar(catxt)-1), sep='', fill = T)
    for (i in cats) {
      cat('\nVariable:', names(df)[i], '\n')
      print(freq(df[,i], plot = F))
    }
  }
  if (length(nums) > 0) {
    nutxt <- '\nDescription of numeric variables'
    cat(nutxt, '\n')
    cat(rep('=', nchar(nutxt) - 1), sep='', fill = T)
    auxfun <- function(x, ...) {
    sumvar <- c(mean(x, ...), sd(x, ...), median(x, ...), range(x, ...))
    names(sumvar) <- c('Mean', 'SD', 'Median', 'Min', 'Max')
    return(round(sumvar, 1))
    }
    for (j in nums) {
      cat('\nVariable:', names(df)[j], '\n')
      print(auxfun(df[ ,j], ...))
    }
  }
 }

z.test <- function(table, n = NULL, tail = "two.sided", correct = F) {
```

```
  r <- prop.test(table, n = n, alternative = tail, correct = correct)
  res <- round(c(r$estimate*100,
                 (r$estimate[1] - r$estimate[2])*100,
                 r$conf.int*100,
                 r$p.value),
               3)
  names(res)[3:6] <- c("Difference", "CI.lo", "CI.up", "p-value")
  res
}
```

D.2 Data preparation and several analysis

We had to suitably prepare data for a multi-state analysis.

```
## ------------------------------------------------------------------------------
## 1.- LOAD THE DATA -------------------------------------------------------------
library(mstate)
load('G:/pankreatitis/Datu-basea/pancData.RData')
str(pancdata)
dim(pancdata)
## ------------------------------------------------------------------------------

## ------------------------------------------------------------------------------
## 2.- DATA PREPARATION ----------------------------------------------------------
## (a) transition matrix ---------------------------------------------------------
tmat <- transMat(x = list(c(2,3), c(3,4), c(), c()),
names = c('ICU', 'Hospital', 'Death', 'Home'))
paths(tmat)

pancdata$dtime <- with(pancdata, ifelse(death == 'Muerto',
                                as.numeric(difftime(date.death, entry.uci,
                                                    units = 'days')),
                                NA))
pancdata$ihtime <- with(pancdata, as.numeric(difftime(out.uci,
                                        entry.uci, units = 'days')))
pancdata$hhtime <- with(pancdata, ifelse((is.na(dtime) & !is.na(out.hosp)),
                                         as.numeric(difftime(out.hosp, entry.uci,
                                                  units = 'days')),
                                         NA))
pancdata$hhtime <- with(pancdata, ifelse(is.na(hhtime), dtime, hhtime))
head(pancdata$surgtime)

# Fill NA-s
pancdata$dtime <- with(pancdata, ifelse((is.na(dtime) & !is.na(out.hosp)),
                                       as.numeric(difftime(out.hosp, entry.uci),
                                                          units = 'days'),
                                       dtime))
pancdata$dtime <- with(pancdata, ifelse(is.na(dtime),
                                as.numeric(difftime(as.Date('2017-08-31'),
                                                    entry.uci,
                                                    units = 'days')),
                                dtime))
pancdata$ihtime <- with(pancdata, ifelse(is.na(ihtime), dtime, ihtime))

# status variables
pancdata$ihstatus <- as.numeric(!is.na(pancdata$out.uci))
pancdata$dstatus <- as.numeric(pancdata$death == 'Muerto')
pancdata$hhstatus <- as.numeric(!is.na(pancdata$out.hosp))
```

```
## (b) To LONG FORMAT ------------------------------------------------------------
## -------------------------------------------------------------------------------
covs <- c('id.hist', 'gender', 'age', 'period', 'bmi', 'etiology', 'ventmech', 'hemo',
          'embo', 'days.vent', 'days.hemo', 'date.embo', 'death', 'surg', 'date.surg',
          'surgtime', 'apache', 'ct', 'death.where', 'feeding', 'loc.comp', 'ihtime')
panclong <- msprep(time = c(NA, 'ihtime', 'dtime', 'hhtime'),
                   status = c(NA, 'ihstatus', 'dstatus', 'hhstatus'),
                   data = pancdata, trans = tmat, keep = covs)

print(panclong, trans = T)
events(panclong)

# adding transition specific covariates
panclong <- expand.covs(panclong, c(covs[-c(1, 15)], 'id'), append = T, longnames = F)
head(panclong)
```

For the non-parametric analysis we have made use of the subsequent code,

```
## -------------------------------------------------------------------------------
## 3.- NON-PARAMETRIC ANALYSIS ---------------------------------------------------
c0 <- coxph(Surv(Tstart, Tstop, status) ~strata(trans), data = panclong,
            method = 'breslow')
msf0a <- msfit(object = c0, sub.panclong, vartype = 'aalen', trans=tmat)

summary(msf0a)
vH1 <- msf0a$varHaz
head(vH1[vH1$trans1 == 1 & vH1$trans2 == 1, ])
tail(vH1[vH1$trans1 == 1 & vH1$trans2 == 1, ])
head(vH1[vH1$trans1 == 2 & vH1$trans2 == 2, ])
tail(vH1[vH1$trans1 == 2 & vH1$trans2 == 2, ])
head(vH1[vH1$trans1 == 4 & vH1$trans2 == 4, ])
tail(vH1[vH1$trans1 == 4 & vH1$trans2 == 4, ])

# PLOT: Cumulative transition intensities ---------------------------------------
windows(width=12)
par(las = 1, bty='l', font = 2, font.axis = 2, font.lab = 4,
    cex.axis = 1.6, cex.lab = 1.6)
plot(msf0a,lwd=3, xlab = 'Days from ICU entrance', col = c(2, 4, 4, 5),
     lty = c(1, 1, 2, 1), xlim = c(0, 120), ylim=c(0,4.5))
savePlot('G:/pankreatitis/Irudiak/NPcumhaz', type = 'pdf')
# -------------------------------------------------------------------------------

# Transition probability, initial time s=0.5 ------------------------------------
pt0a <- probtrans(msf0a, predt = 0.5, method = 'aalen') # predt: the starting time
summary(pt0a, from = 1) # from starting state
pt0a[[1]][22,]; pt0a[[2]][22,]; pt0a[[3]][22,]; pt0a[[4]][22,]
# Transition probability, initial time s=7 --------------------------------------
pt0a7 <- probtrans(msf0a, predt = 7, method = 'aalen')

# PLOT: Transition probabilities ------------------------------------------------
windows(width=15)
par(mfrow=c(1,2), las = 1, bty='l', font = 2, font.axis = 2, font.lab = 4,
    cex.axis = 1.6, cex.lab = 1.6, cex.main=1.6, mar=c(5,5,4,5))
ord <- 1:4
plot(pt0a, ord = ord, xlab = 'Days from ICU entrance',
     las = 1, type = 'single', col = c(3,2,'springgreen4',5), xlim=c(0,100), lwd=3,
     legend.pos = c(x,y))
abline(v=21, lty=2, lwd=1.8)
plot(pt0a, from=2, ord = ord, xlab = 'Days from ICU entrance',
```

```
     las = 1, type = 'single', col = c(3,2,'springgreen4',5), xlim=c(0,100), lwd=3,
     legend.pos = c(x, y))
abline(v=21, lty=2, lwd=1.8)
savePlot('G:/pankreatitis/Irudiak/NPprob2', type = 'pdf')
# ------------------------------------------------------------------------------
```

Following a part of the stepwise analysis is shown,

```
## ------------------------------------------------------------------------------
## 4.- STEPWISE ANALYSIS ---------------------------------------------------------
# 0.Null model -----------------------------------------------------------------
(c.null <- coxph(Surv(time, status)~strata(trans), data=panclong, method='breslow'))

# 1. Univariate ----------------------------------------------------------------
# (a) age ----------------------------------------------------------------------
(c.a2 <- coxph(Surv(time, status)~age.1 + age.2 + age.4 + strata(trans),
                  data=panclong, method = 'breslow'))
anova(c.null, c.a2, test='LRT'); -2* logLik(c.a2); AIC(c.a2)

# (b) gender -------------------------------------------------------------------
(c.b2 <- coxph(Surv(time, status)~gender.1 + gender.2 + gender.4 + strata(trans),
               data=panclong, method = 'breslow'))
anova(c.null, c.b2, test='LRT'); -2 logLik(c.b2); AIC(c.b2)

# (c) etiology -----------------------------------------------------------------
(c.c2 <- coxph(Surv(time, status)~etiology1.1 + etiology1.2 + etiology1.4 +
               etiology2.1 + etiology2.2 + etiology2.4 +
               etiology3.1 + etiology3.2 + etiology3.4 +strata(trans),
               data=panclong, method = 'breslow'))
anova(c.null, c.c2, test='LRT'); -2*logLik(c.c2); AIC(c.c2)

# (d) bmi ----------------------------------------------------------------------
(c.d2 <- coxph(Surv(time, status)~bmi.1 + bmi.2 + bmi.4 + strata(trans),
               data=panclong, method = 'breslow'))
anova(c.null, c.d2, test='LRT'); -2*logLik(c.d2); AIC(c.d2)

# (e) apache -------------------------------------------------------------------
(c.e2 <- coxph(Surv(time, status)~apache.1 + apache.2 + apache.4 + strata(trans),
               data=panclong, method = 'breslow'))
anova(c.null, c.e2, test='LRT'); -2*logLik(c.e2); AIC(c.e2)

# (g) feeding ------------------------------------------------------------------
(c.g2 <- coxph(Surv(time, status)~feeding1.1 + feeding1.2 + feeding1.4 +
                                  feeding2.1 + feeding2.2 + feeding2.4 + strata(trans),
                                  data=sub.panclong, method = 'breslow'))
anova(c.null, c.g2, test='LRT'); -2*logLik(c.g2); AIC(c.g2)

# (h) ihtime -------------------------------------------------------------------
(c.h2 <- coxph(Surv(time, status)~ihtime.4 + strata(trans), data=panclong,
               method = 'breslow'))
anova(c.null, c.h2, test='LRT'); -2*logLik(c.h2); AIC(c.h2)


# 2. Feeding + Var. ------------------------------------------------------------
(c.bat <-c.g2)
anova(c.null, c.bat, test='LRT'); -2*logLik(c.bat); AIC(c.bat)

# (a) plus apache --------------------------------------------------------------
(c.bat1 <- update(c.bat, ~. + apache.1 + apache.2 + apache.4))
anova(c.bat, c.bat1, test='LRT'); -2*logLik(c.bat1); AIC(c.bat1)
```

```
# (b) plus age ------------------------------------------------------------------
(c.bat2 <- update(c.bat, ~. + age.1 + age.2 + age.4))
anova(c.bat, c.bat2, test='LRT'); -2*logLik(c.bat2); AIC(c.bat2)

# (c) plus etiology -------------------------------------------------------------
c.bat3 <- update(c.bat, ~. + etiology1.1 + etiology1.2 + etiology1.4 +
                           etiology2.1 + etiology2.2 + etiology2.4 +
                           etiology3.1 + etiology3.2  + etiology3.4)
anova(c.bat, c.bat3, test='LRT'); -2*logLik(c.bat3); AIC(c.bat3)

# (d) plus gender ---------------------------------------------------------------
c.bat4 <- update(c.bat, ~. + gender.1 + gender.2 + gender.4)
anova(c.bat, c.bat4, test='LRT'); -2*logLik(c.bat4); AIC(c.bat4)

# (e) plus BMI ------------------------------------------------------------------
c.bat5 <- update(c.bat, ~. + bmi.1 + bmi.2 + bmi.4)
anova(c.bat, c.bat5, test='LRT'); -2*logLik(c.bat5); AIC(c.bat5)

# (f) plus ihtime.4 -------------------------------------------------------------
c.bat6 <- update(c.bat, ~. + ihtime.4)
anova(c.bat, c.bat6, test='LRT'); -2*logLik(c.bat6); AIC(c.bat6)
```

The final model,

```
## ------------------------------------------------------------------------------
## THE FINAL MODEL ---------------------------------------------------------------
## Way 1 (all transitions together) ----------------------------------------------
(c.final <- coxph(Surv(time,status)~
                     feeding1.2 + feeding2.2 + apache.2 + surgery.4 + apache.4 + bmi.4 +
                  apache.3 + surgery.5 +
                  ihtime.8 + surgery.10 + strata(strata),
                  data=panclong, method='breslow'))    # strata, each transition

## Way 2 (separately) ------------------------------------------------------------
# Model 1 -----------------------------------------------------------------------
(model1 <- coxph(Surv(time,status)~
                 feeding1.2+feeding2.2 + apache.2 +
                 surgery.4 + apache.4 + bmi.4,
                 data=panclong, subset=strata==2, method='breslow')) # subsetting data

# Model 2 -----------------------------------------------------------------------
(model2 <- coxph(Surv(time,status)~
                 apache.3 + surgery.5,
                 data=panclong, subset=strata==3, method='breslow')) # subsetting data
# Model 3 -----------------------------------------------------------------------
(model3 <- coxph(Surv(time,status)~
                 ihtime.8 + surgery.10,
                 data=panclong, subset=strata==4, method='breslow')) # subsetting data
```